The pallidopyramidal syndromes: nosology, aetiology and pathogenesis

Eleanna Kara, John Hardy, and Henry Houlden

INTRODUCTION

The term pallidopyramidal degeneration (PPD) was first introduced by Davison in 1954 [1] who described a series of five patients presenting with the triad of progressive parkinsonism, spasticity and dystonia combined with pyramidal and pallidal lesions and blue discolouration of the globus pallidus following the initial report by Hunt in 1917 [2] of a single case with juvenile parkinsonism and eosinophilic spheroidal structures. Subsequently, Hallervorden and Spatz in 1992 reported a family with five affected sisters with brown discoloration of the globus pallidus [3], a syndrome that was named Hallervorden–Spatz syndrome.

During the past decade, the advent of genetic technologies has allowed a more systematic delineation of the clinical presentations and genetic underpinnings of PPD starting with the identification of the first mutations in PANK2 [4], a finding that led to the renaming of this disease class to neurodegeneration with brain iron accumulation (NBIA) [4,5]. Despite the fact that a molecular diagnosis and modern neuropathological analysis is not possible for the initial cases described by Davison due to the lack of preserved tissue and blood, it is likely that the brown–blue discoloration of the globus pallidus represents gross iron accumulation and the eosinophilic formations neuroaxonal spheroids, and that all belong to the modern disease entity of NBIA (Fig. 1a).
In this review, we argue that the use of the term NBIA is not ideal and suggest that the more general term pallidopyramidal syndromes (PPS) conceived by Davison would perhaps be more appropriate [6]. In this context, we also suggest a modified classification system better reflecting the clinical and pathological phenotypes associated to PPS. Finally, we outline possible disease mechanisms providing a mechanistic basis for some of the features unique to PPS that were first highlighted by Davison, and suggest a model tying the pathogenesis of lysosomal storage diseases (LSD), Parkinson’s disease, and PPS.

**CLASSIFICATION OF PALLIDOPYRAMIDAL SYNDROMES**

At present, according to the OMIM classification system, a disease is classified as NBIA based on the clinical features including Davison’s PPD triad (Fig. 1b), and gross iron accumulation on T2 MRI. Further classification in four subtypes depends on the pattern of iron accumulation on MRI, and on the underlying mutated genetic locus (Table 1).

**Caveats of the current classification system**

The current classification system is far from ideal for two reasons:

1. The use of iron accumulation as a classification criterion is debatable. Iron accumulation is not a consistent finding among diseases with otherwise indistinguishable clinical presentations [7–10] leading to the use of the oxymoron term ‘NBIA without brain iron’ [10]. Also, the importance of iron for disease pathogenesis and progression remains elusive [10], especially as this has been reported in various seemingly unrelated disorders and even in healthy individuals [10–12].

2. The use of a classification system based on mutated genetic loci has two weaknesses. First, as the complete genetic landscape of NBIA is unknown, there are several ‘idiopathic’ syndromes that are not included in the current classification system (Fig. 1c). Second, patients with mutations in the same gene often present with substantially divergent clinical features [8,13].

Taking into account these weaknesses, we suggest that at present a clinical and pathological classification system of NBIA would be more suitable for clinical practice.

**Pallidopyramidal syndromes: Proposed clinical classification system**

In our suggested classification system, a disease must be characterized by Davison’s triad with or without iron accumulation on MRI to be classified as PPS. Further sub-classification is based on the age at onset of symptoms as this feature can serve as a starting point to prioritise genetic testing (Table 2A).

1. Infantile PPS (iPPS): iPPS presents before the age of 2 years and includes pantothenate kinase associated neurodegeneration (PKAN) [4] and hereditary dopamine transporter deficiency syndrome (HDTDS) [14]. The symptoms at presentation are unspecific with feeding difficulties, irritability and/or developmental delay, followed by the development of severe movement disorders [15]. Optic nerve atrophy and cognitive decline are seen in infantile neuroaxonal dystrophy (INAD), whereas cognition is maintained in HDTDS [14,16]. Disease progression is usually rapid resulting in death in approximately 10 years [17].

2. Juvenile PPS (jPPS): jPPS has an onset with spasticity in FBXO7-associated neurodegeneration (PKAN) [4] and hereditary dopamine transporter deficiency syndrome (HDTDS) [14]. The symptoms at presentation are unspecific with feeding difficulties, irritability and/or developmental delay, followed by the development of severe movement disorders [15]. Optic nerve atrophy and cognitive decline are seen in infantile neuroaxonal dystrophy (INAD), whereas cognition is maintained in HDTDS [14,16]. Disease progression is usually rapid resulting in death in approximately 10 years [17].

Taking into account these weaknesses, we suggest that at present a clinical and pathological classification system of NBIA would be more suitable for clinical practice.
The recently described β-pro- 

teller protein-associated neurodegeneration

(BPAN) is a distinct form of jPPS as onset is at
early childhood with global developmental
delay accompanied by iron accumulation on
MRI preceding the development of prominent
pallidopyramidal signs [24&&,25,26&&,27&&,28&&].

(3) Adult PPS (aPPS): aPPS has an onset after the age
of 18–20 years and psychiatric features as a
presenting sign are common followed by the
development of rapidly progressive movement
disorders [8,15,29,30].

Often, a differential diagnosis has to be made
from phenocopies (atypical, usually milder presen-
tations of syndromes caused by mutations in differ-
ent genetic loci, reviewed in [9]). However, we do
not include these in the suggested classification
system as they probably do not fit in the nosological
entity originally described by Davison and we thus

Table 1. Current OMIM classification of neuro-
degeneration with brain iron accumulation
syndromes

| NBIA | Disease |
|------|---------|
| NBIA 1 | Pantothenate kinase-associated neurodegeneration (PKAN)[PANK2] |
| NBIA 2A | Infantile neuroaxonal dystrophy (INAD)[PLA2G6] |
| NBIA 2B | Atypical neuroaxonal dystrophy (PLA2G6) |
| NBIA 3 | Neuroferritinopathy (FTL) |
| NBIA 4 | ATP13A2 |
| Not classified yet | C19orf12 |

\[1919 \quad 1922 \quad 1954 \quad 2001 \quad 2006 \quad 2008 \quad 2009 \quad 2010 \quad 2012\]
use the term PPS only in the context of NBIA syndromes.

**PATHOLOGY OF PALLIDOPYRAMIDAL SYNDROMES: INSIGHTS INTO PATHOGENETIC MECHANISMS AND IMPLICATIONS FOR THE PROPOSED PATHOLOGICAL CLASSIFICATION SYSTEM**

As only a small number of PPS cases have come to pathology, our knowledge on the pathological features of PPS is incomplete. However, there are two main findings present in all PPS studied (PKAN, PLA2G6-associated neurodegeneration – PLAN, PLAA2G6); iron-laden pigmentation and spheroids with a predilection for pallidal involvement in PKAN [31,32] but a wider lesion distribution in the remaining syndromes [33,34,35]. α-Synuclein accumulation [36,37] is an additional feature in a subset of PPS (PLAN, MPAN) [33,34,35]. Here, we discuss the potential pathogenic processes underpinning these lesions and their implications for our suggested pathological classification system.

**α-Synuclein and pallidopyramidal syndromes**

Although α-synuclein deposition consistently occurs in various neurodegenerative diseases it is still unclear whether this is the primary event driving disease pathogenesis or is just an epiphenomenon [38].

Here, drawing mainly from studies on Parkinson’s disease, we argue that most recent evidence implicates lysosomal dysfunction and/or lipid abnormalities in the aggregation and spreading of α-synuclein and then discuss the implications of this observation for the pathogenesis of PPS.

**Lewy body formation is probably caused by lysosomal dysfunction**

Lewy bodies have been reported in four disease categories: Parkinson’s disease, PPS, LSD and dementia with Lewy bodies. Interestingly, the common denominator in most of these situations with α-synuclein accumulation appears to be lysosomal dysfunction:

1. Lewy body pathology [36] is an important pathological feature of Parkinson’s disease observed in most genetic forms, and in several idiopathic cases [39]. However, Lewy bodies in Parkinson’s disease consistently occur on two occasions: when the primary genetic defect lies in the glucocerebrosidase (GBA) or in the α-synuclein SNCA gene [40].

   (a) Numerous studies have demonstrated that GBA is a lysosomal enzyme [41,42,43], a role which is further emphasized by the fact

---

**Table 2A. Suggested PPS clinical classification system**

| Infantile PPS | Juvenile PPS | Adulthood PPS |
|---------------|--------------|---------------|
| PLA2G6-associated neurodegeneration (PLAN) (INAD) (PLA2G6) | Typical PKAN (PANK2) | Adulthood PLAN (PLA2G6) |
| Hereditary dopamine transporter deficiency syndrome (SLC6A3) | Childhood PLAN (PLA2G6) | Atypical PKAN (PANK2) |
| Typical Pantothenate kinase-associated neurodegeneration (PKAN) (PANK2) | Fatty acid-associated neurodegeneration (FA2H) | Neuroferritinopathy (FTI) |
| ‘Idiopathic’ PPS | Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP) (PANK2) | ‘Idiopathic’ PPS |
| | Mitochondrial membrane protein associated neurodegeneration (MPAN) (C19orf12) | |
| | Karak syndrome (PLA2G6) | |
| | Kufor Rakeb syndrome (ATP13A2) | Atypical PKAN (PANK2) |
| | FBXO7-associated neurodegeneration (FBXO7) | |
| | Hereditary Spastic Paraplegia with thinning of the corpus callosum (HSP-TCC) (SPG11) | |
| | ‘Idiopathic’ PPS | |
| | Beta-propeller protein-associated neurodegeneration (BPAN) (WDR45) | |
that homozygous mutations in GBA cause Gaucher’s disease, a LSD. Heterozygous mutations in GBA are the strongest risk factor associated to the development of Parkinson’s disease [44] and dementia with Lewy bodies [45,46**]. Interestingly, Lewy bodies is the characteristic feature that ties these seemingly unrelated disorders as they are observed in nearly all cases that come to pathology [40**,47–50]. Recently, a model based on experimental evidence was suggested to explain this relation between GBA and α-synuclein: glycosylceramide (GlcCer), the substrate to GBA, can stabilize α-synuclein oligomers which in turn inhibit GBA function, cause GlcCer accumulation and further attenuate α-synuclein aggregation [51,52].

(b) SNCA multiplications [53] and point mutations [54**,55**,56,57**–59**] are always related to Lewy-body pathology [40**]. In the former case, the causative link is straightforward: increased transcription results in increased expression levels. In the second case, however, the exact mechanisms resulting in α-synuclein accumulation are not obvious though it is thought that lysosomal chaperon-mediated autophagy (CMA) could be impaired [60–62,63*,64*]. A similar effect is also caused by α-synuclein accumulation [65] probably resulting in a positive feedback loop [66*].

(2) ATPI3A2, a gene encoding a lysosomal protein [67] mutated in PPS [7,68], Parkinson’s disease [45,69–71] and LSD [72**,73,74], has recently emerged as an important lysosomal factor involved in α-synuclein homeostasis and as a component of Lewy bodies [7,75**,76]. In addition, the lysosomal dysfunction caused by ATPI3A2 mutations has been shown to directly cause α-synuclein accumulation [77*,78**].

(3) α-Synuclein homeostasis appears to be affected in LSD which are often characterised by Lewy bodies in neuropathology [79]. Neuronal ceroid lipofuscinosis (NCL) type 10, which is one of these LSD with Lewy bodies [80,81], is caused by mutations in cathepsin D (CSTD) that mediates α-synuclein degradation [82].

On the contrary, Lewy bodies occasionally occur in some cases without a clear lysosomal involvement. Parkinson’s disease and PPS caused by mutations in mitochondrial proteins parkin [40**,83–88,89*,90*], PINK1 [40*,91], PLA2G6 [35*] and C19orf12 [33,34**], respectively, frequently have Lewy-body pathology. Lewy bodies are also described in most cases with LRRK2 mutations [40**], a protein whose precise function is currently unknown. Finally, Lewy bodies are frequent in ‘sporadic’ Parkinson’s disease in similar distribution and severity to GBA-associated disease [39]. The significance of these observations and the relation of α-synuclein accumulation to mitochondrial dysfunction are discussed later.

Interactions between α-synuclein and lipids both within the lysosomal context [51] and the cytoplasm [92**,93] also seem to underlie α-synuclein homeostasis. Such extensive α-synuclein–lipid interactions are in keeping with the highlighted frequent involvement of ceramide metabolism pathways in parkinsonian disorders with Lewy Bodies in neuropathology [94]. Given that GlcCer interactions have been shown to stabilize α-synuclein oligomers, we can hypothesize that similar α-synuclein–lipid interactions in the cytoplasm could have similar consequences.

Why are Lewy bodies absent from some pallidopyramidal syndromes but present in others?

Pathologically, PPS can be distinguished into two categories based on the presence or absence of α-synuclein accumulation: PKAN and Neuroferritinopathy are characterized by well localized defects in the globus pallidus [31,32*] and absence of Lewy bodies, contrary to PLAN [35*] and MPAN [33,34**]. We hypothesize that PKAN and Neuroferritinopathy are well localized diseases due to the absence of α-synuclein accumulation and the accompanying hypothesized self-perpetuating mechanism of disease spread [95**,96,97*,98,99*,100,101**,102–104, 105*,106**,107–111,112*]: the defect initiates from the globus pallidus but cannot spread to other brain regions due to the absence of α-synuclein involvement. As recent evidence implicates lysosomal dysfunction and/or lipid abnormalities in the aggregation and spreading of α-synuclein, this observation has two possible implications for the pathogenic mechanisms of PKAN:

(1) Probably, lysosomal dysfunction is not a primary event in the pathogenesis of PKAN.

(2) The ceramide lipid metabolism defects observed in PKAN are unlikely to affect α-synuclein homeostasis: Pantothenate kinase 2 (PANK2) encoded by the PANK2 gene, is probably an exclusively mitochondrial enzyme [113,114*] thus placing a physical barrier between lipids and (cytoplasmic) α-synuclein.
Contrary to PKAN, PLAN is characterised by widespread Lewy bodies in neuropathology [35*]. iPLA2 beta which is encoded by the *PLA2G6* gene, is an enzyme involved in phospholipid hydrolysis with implications for a wide range of cellular functions [115**] probably not necessarily limited to the mitochondria; thus, lipid accumulation caused by iPLA2 beta inactivation could be responsible for the initiation of α-synuclein misfolding and spreading.

**Neuroaxonal spheroids: a mitochondrial trafficking defect?**

Neuroaxonal spheroids are mysterious formations present in various serious neurodegenerative diseases including PKAN [31,32*], MPAN [33,34**], Neuroferritinopathy [116,117], Wilson’s disease [115**], progressive supranuclear palsy-pallidonoigro-tylossial atrophy variant (PSP-PNLA) [118], PLAN [35*], hereditary diffuse leukoencephalopathy with spheroids (HDLS) [119,120*,121**], pigmented orthochromatic leukodystrophy (POLD) [122**], and traumatic brain injury [31]; however, these are also observed in healthy, aged individuals [123]. Even though neuroaxonal spheroids have not been ultrastructurally studied in genetically confirmed cases and systematically compared between various diseases, limited electron microscopy studies on nongenetically confirmed HDLS and on mouse models of *PLA2G6* have indicated that these structures likely contain mitochondria [124–126] in addition to other molecules [31,32*,35*,119]. Given the similarities in the staining patterns of the spheroids between diseases, it is likely that they represent identical or highly homologous structures, a remarkable finding given the diversity in clinical presentations of associated diseases.

As neuroaxonal spheroids are present in such a variety of serious neurodegenerative diseases, the mechanisms underlying their formation are intriguing. Here, we hypothesize that spheroids could result from impaired mitochondrial trafficking as a reaction to severe neuronal damage drawing from evidence provided from the study of PKAN.

(1) Specifically in the case of PPS, perhaps their formation stems from a primary mitochondrial dysfunction, a relationship that would seem more clear and convincing in PKAN. As mitochondria heavily rely on CoA provision for energy generation, it is expected that *PANK2* mutations would have a devastating effect on mitochondrial integrity [127**]. The increased number of large degenerate mitochondria [127**] could result in the overload of the macroautophagy pathway with the formation of large, indigestible autophagosomes that cannot be uptaken by the lysosomes [128]; thus, neuroaxonal spheroids could represent these indigestible autophagocytic vesicles. Alternatively, damaged mitochondria could impinge on lysosomal function indirectly through impaired microtubule trafficking [129**,130**].

(2) Mitochondrial trafficking impairment could occur secondarily to mitochondrial defects. It has been recently shown that Miro, a mitochondrial trafficking protein [131,132], is selectively targeted by PINK1 and parkin in mitochondrial damage in order to halt mitochondrial...
trafficking within neuraxons \([133–135,136]\) and that spheroid formation is triggered in the absence of parkin \([137]\). Thus, severe mitochondrial damage could trigger this process en masse, holding mitochondria within neuraxons and initiating neuroaxonal spheroid formation \([31,32]\). This hypothesis is supported by the observation of tau within the spheroids \([31,32,35]\).

![Figure 2](image.png)

**Figure 2.** Spheroidopathies. MPAN, Mitochondrial membrane protein associated neurodegeneration; PKAN, Pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration.

**Implications of neuropathological studies for pathological classification of pallidopyramidal syndromes**

As neuroaxonal spheroids and Lewy bodies are the two characteristic neuropathological features that have shed light into the pathogenetic mechanisms of PPS, an attempted neuropathological classification should probably revolve around these two features with four categories reflecting the presence

| Table 3. Characteristic neuropathological features of pallidopyramidal syndromes (PPS) |
|---------------------------------|-----------------------------------|-----------------------------------|
| PPS                             | Characteristic neuropathological features | Reference |
| PKAN                            | a) Isolation of lesions in the GP | \([31,32]\) |
|                                 | b) Minimal involvement of the SN | |
|                                 | c) Large and small spheroids strongly APP positive | |
|                                 | d) Hemosiderin deposition in neurons, astrocytes and in perivascular region | |
| PLAN                            | a) Extensive tau deposition | \([35]\) |
|                                 | b) LBs | |
|                                 | c) SN depletion | |
|                                 | d) Cerebral and cerebellar atrophy | |
|                                 | e) Neuroaxonal spheroids | |
|                                 | f) Widespread distribution of lesions (spinal cord, basal ganglia) | |
| MPAN                            | a) Widespread pathological alterations | \([33,34]\) |
|                                 | b) LBs | |
|                                 | c) Tau pathology | |
|                                 | d) Axonal spheroids | |
|                                 | e) Iron in astrocytes and macrophages | |
| Neuroferritinopathy             | a) Cystic cavitation of GP | \([115,116,117]\) |
|                                 | b) Iron deposition | |
|                                 | c) Spheroids | |

APP, amyloid precursor protein; GP, globus pallidus; LBs, Lewy Bodies; MPAN, Mitochondrial membrane protein associated neurodegeneration; PKAN, Pantothenate kinase-associated neurodegeneration; PLAN, PLA2G6-associated neurodegeneration; SN, substantia nigra.
or absence of α-synuclein accumulation and/or Lewy bodies (Table 2B). In addition, as neuroaxonal spheroids are a common feature of several neurodegenerative diseases, we suggest the establishment of a separate disease category of ‘spheroidopathies’ (Table 2B, Fig. 2, Table 3).

**DISEASE MODEL HYPOTHESIS: THE ‘PARKINSONIAN MITOCHONDRIAL–LYSOSOMAL TRIANGLE’**

There appears to be a clear relationship between PPS, Parkinson’s disease and LSD clinically [9,138,139], pathologically [33,35,40,41] and genetically [7,19,44,68,71,72,73,74,140,141,142] indicating that their pathogenic pathways are perhaps also linked.

As genetic and functional studies have demonstrated, defects in two main organelles can cause Parkinson’s disease, PPS or LSD: mitochondria [127,144–151,152,153,154] and lysosomes [79,142,155,156]. Interestingly, for some of the mutated molecules involved in the dysfunction of these two organelles, there is functional and neuropathological evidence mapping them clearly in one of the two pathways. However, for the rest there seems to be an overlap: even though for each mutated gene there is strong functional evidence that only one of the two organelles should be affected, there are circumstantial pathological features indicating that perhaps the second organelle is affected too (Table 4).

Thus, in general, Lewy bodies consistently occur in cases with mutations in lysosomal enzymes whereas these are found only occasionally in relation to mutations in mitochondrial proteins. This observation would support the hypothesis that mitochondrial dysfunction does not directly cause α-synuclein accumulation; indeed, to date, there is not strong enough functional evidence that

### Table 4. Molecules that genetic studies have implicated in the pathogenesis of pallidopyramidal syndromes, Parkinson’s disease and Lysosomal storage disorders

| Molecule  | Organelle of function | Function                                      | Usual neuropathological features | Findings inconsistent with the primary function of the molecule (assuming that LB formation is secondary to lysosomal dysfunction) |
|-----------|------------------------|-----------------------------------------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Parkin    | Mitochondria           | Ubiquitin ligase targeting mitochondrial membrane proteins [144–151,152,158] | SN cell loss without LBs        | Occasional presence of LBs [157**]                                                                                   |
| PINK1     | Mitochondria           | Regulation of parkin in mitochondria [144–151,152] | Unknown                         | LBs in the single case studied                                                                                       |
| C19orf12  | Mitochondria           | Limited information                            | LBs, spheroids, tau              | LBs                                                                                                                |
| iPLa2 beta| Mitochondria           | Phospholipid hydrolysis                        | LBs, spheroids, tau              | LBs                                                                                                                |
| ATP13A2   | Lysosomes              | SNCA homeostasis                               | Unknown                         | Mitochondrial abnormalities [160**]. Mutations can cause PPS, PD or Lysosomal storage disorders [7,68,71,72,73,74]. |
| Glucocerebrosidase | Lysosomes [41,42,43,51] | Pathway of CoA synthesis                      | LBs                             |                                                                                                                     |
| PANK2     | Mitochondria           | Pathway of CoA synthesis                      | Spheroids                       | –                                                                    |
| WDR45     | Limited information    | Vesicular trafficking Autophagy [24**,26**]    | Unknown                         | Limited information                                                                                                 |
| VPS35     | Limited information    | Vesicular trafficking Autophagy [161,162]      | No LBs in a single case studied  | [161,162,164]                                                                                                       |
| LRRK2     | Inconclusive evidence  | Autophagy [165**,166**,167**]                  | Variable (LBs, tau, TDP43 [171] | Limited information                                                                                                 |
| α-synuclein| Inconclusive evidence  | Synaptic function, microtubule trafficking (reviewed in [92**]) | LBs                             | –                                                                    |

LB, Lewy body; PD, Parkinson’s disease; SN, substantia nigra.

*For full references concerning the pathological features see [40]**.

*Even though GBA mutations can cause both Parkinson’s disease and Lysosomal storage disorders, the recent identification of a variant (E326K) that causes exclusively Parkinson’s disease both in homozygosis and in heterozygosis [172**] suggests a separate regulatory rather than metabolic effect of glucocerebrosidase in the pathogenesis of Parkinson’s disease [173*,174*]; certainly though, this observation does not disassociate Parkinson’s disease development from lysosomal dysfunction.
mitochondrial dysfunction impacts directly on α-synuclein homeostasis [175,176], though there is some evidence supporting the opposite [98,175,177,178,179,180,181].

Such an overlap in pathologies would suggest that there is a functional link between lysosomes and mitochondria and that unknown events (or perhaps even stochasticity) could shift the balance between the two pathways and some well-determined genetic forms of Parkinson’s disease develop inconsistent pathological features. We term this functional continuum ‘Parkinsonian mitochondrial–lysosomal triangle’ and suggest that PPS and LSD lie in the extreme ends of this triangle with Parkinson’s disease as an intermediate form of disease (Fig. 3a).

If this theory holds true, we can make two interesting hypotheses:

1. Parkinson’s disease should share some pathological features of LSD. Although no lipofuscin inclusions have been observed in Parkinson’s disease, somebody could argue that Lewy bodies represent a form of lysosomal inclusions as they contain ATP13A2 [75], GBA [182] and numerous lysosomal molecules [183,184].

2. How can lysosomes and mitochondria be functionally connected? Though the exact nature of this link is unknown, it is thought to take the form of mitophagy [185] and to be bidirectional (Fig. 3b). Indeed, there is evidence suggesting that dysfunctional lysosomes ‘attack’ mitochondria in ATP13A2 patient fibroblasts [160] and that lysosomal dysfunction could result in an accumulation of dysfunctional mitochondria in mouse models of LSD [186]. Conversely, damaged mitochondria can impact on autophagy through impaired microtubule-mediated vesicular trafficking resulting in a more generalized lysosomal dysfunction (including inhibition of α-synuclein degradation) [129,157]. The molecules most recently implicated in the pathogenesis of Parkinson’s disease and PPS, VPS35 [161,162,187–190] and

**FIGURE 3.** (a) The Parkinsonian mitochondrial–lysosomal triangle: Venn diagram depicting that pallidopyramidal syndromes (PPS), lysosomal storage disorders (LSD) and Parkinson’s disease overlap pathologically, genetically and/or clinically. The orange arrow in the bottom indicates that the mitochondrial–lysosomal complex could form a functional continuum defects along which can result in an array of disorders, with PPS and LSD being at the extreme ends and Parkinson’s disease lying in the middle. Blue arrows indicate that lipid metabolism could be implicated in all three entities in different ways (intramitochondrially, intralysosomally and cytoplasmically/cell membrane). GBA is placed in the overlap between LSD and Parkinson’s disease as heterozygous mutations result in Parkinson’s disease but homozygous in LSD. SNCA is also placed in the overlap as α-synuclein pathology is observed in both Parkinson’s disease and LSD. SPG11 is placed in the overlap between PPS and PD as SPG11 can have a clinical presentation very similar to either PD or PPS. ATP13A2 is placed in the overlap between PPS, Parkinson’s disease and LSD as mutations can cause all three disease entities (in Parkinson’s disease heterozygous mutations appear to be a risk factor). Leukoencephalopathies are placed in the bottom between PPS and LSD as mutations in FA2H can cause both diseases and neuroaxonal spheroids have been reported in relation to both diseases. Also, metachromatic leukodystrophy is both a leukoencephalopathy and a LSD [79]. (b) Simplified diagram depicting the suggested lysosomal–mitochondrial link. This is based on neuropathological reports for carriers of mutations in specific genes and experimental evidence for the functional role of these genes. The rectangle in the bottom shows which types of neuropathology are related to defects in particular molecules (listed on the top of the figure, in relation to their localisation and/or function).
CONCLUSION

We propose a simplified classification of PPS that allows incorporation of the increasing genetic findings. Although the precise pathogenic underpinnings of PPS are far from clear, numerous reports suggest interesting links on multiple levels between PPS, Parkinson’s disease and LSD with a central role for combined mitochondrial and lysosomal dysfunction, a relation which will be further dissected as identification of novel disease-causing genes adds the missing pieces to the puzzle [20].

Acknowledgements

The authors would like to thank the members of the Department of Molecular Neuroscience, Institute of Neurology, UCL for useful discussions. The authors would also like to thank the Medical Research Council (MRC), the National Organisation for Rare Disorders (NORD), the Dystonia Medical Research Foundation (DMRF), the dystonia coalition and the Parkinson’s disease foundation (PDF) for funding their research.

Conflicts of interest

None declared.

Funding disclosure: This work was funded by the Wellcome Trust/MRC Joint Call in Neurodegeneration award (WT089698) to the UK Parkinson’s Disease Consortium (UKPDC) whose members are from the UCL Institute of Neurology, the University of Sheffield and the MRC Protein Phosphorylation Unit at the University of Dundee, the Medical Research Council (MRC), the National Organisation for Rare Disorders (NORD), the Dystonia Medical Research Foundation (DMRF), the dystonia coalition and the Parkinson’s disease foundation (PDF).
27. Kasai-Yoshida E, Kumada S, Yagishita A, et al. First video report of static encephalopathy of childhood with neurodegeneration in adulthood. Mov Disord 2013; 28:397–399.

This is a case report supported by video documentation of a patient with BNAP.

28. Kimura Y, Sato N, Sugaki K, et al. MRI, MR spectroscopy, and diffusion tensor imaging findings in patient with static encephalopathy of childhood with neurodegeneration in adulthood (SENDA). Brain Dev 2012; 35:458–461.

This study reports MRI features of BNAP.

29. Chinnery PF, Crompton DE, Birchall D, et al. Clinical features and natural history of neurofibromatosis caused by the FTLD 480insM mutation. Brain 2007; 130:1110–1119.

30. Pellecchia MT, Valente EM, Cil F, et al. The diverse phenotype and genotype of pantetheine kinase-associated neurodegeneration. Neurology 2005; 64:1810–1812.

31. Krue MC, Hiken M, Gregory A, et al. Novel histopathologic findings in molecularly-confirmed pantetheine kinase-associated neurodegeneration. Brain 2011; 134:947–958.

32. Li A, Paudel R, Johnson R, et al. Pantetheine kinase-associated neurodegeneration is not a synucleinopathy. Neuropathol Appl Neurobiol 2012. doi: 10.1111/j.1365-2990.2012.02699.x.

This study confirms the findings of Krue et al. (2011) that PANK2 mutations are not associated to α-synuclein accumulation.

33. Hess MB, Iuso A, Haack T, et al. Absence of an orphan mitochondrial protein, c19orf12, causes a distinct clinical subtype of neurodegeneration with brain iron accumulation. Am J Hum Genet 2011; 89:543–550.

34. Hogarth P, Gregory A, Krue MC, et al. New NBIA subtype: genetic, clinical, pathological, and radiographic features of MPAN. Neurology 2013; 80:268–275.

This is the first large follow-up study after the identification of mutations in C19orf12 as a cause of NBIA.

35. Paisan-Ruiz C, Li A, Schneider SA, et al. Widespread Lewy body and tau accumulation in childhood and adult onset dystonia-parkinsonism cases with C19orf12 mutations. Brain 2012; 135:814–823.

This study showed that PLA2G6 mutations are associated to α-synuclein and tau accumulation.

36. Spillantini MG, Schmidt ML, Lee VM, et al. Alpha-synuclein in Lewy bodies. Nature 1997; 388:839–840.

37. Goedert M, Spillantini MG, Del Tredici K, Braak H. 100 years of Lewy pathology. Nat Rev Neurosci 2013; 9:13–24.

This review outlines the progress in the understanding of the role of α-synuclein accumulation in the pathogenesis of Parkinson’s disease since the discovery of Lewy bodies.

38. Schütz-Schaefer WJ. Neurodegeneration in Parkinson disease: moving away from Lewy bodies out of focus. Neurology 2012; 79:2298–2299.

This editorial discussed the relevance of Lewy bodies to the pathogenesis of Parkinson’s disease.

39. Parkkinen L, Neumann J, O’ Sullivan SS, et al. Glucocerebrosidase mutations do not cause increased Lewy body pathology in Parkinson’s disease. Mol Genet Metab 2011; 103:410–412.

40. Poulpoudou M, Lewy OA, Alcañiz RN. The neuropathology of genetic Parkinson’s disease. Mov Disord 2012; 27:831–842.

This review article summarises the neuropathological features of genetic forms of Parkinson’s disease.

41. Brady RO, Kanfer J, Shapiro D. The Metabolism of glucocerebrosides. J Biol Chem 2011; 286:28080–28088.

42. Singleton AB, Farrow M, Johnson J, et al. alpha-Synuclein locus triplication causes Parkinson’s disease. Science 2003; 302:841.

43. Proukakis C, Dudzik CG, Brer T, et al. A novel alpha-synuclein missense mutation in parkinson disease. Neurology 2013; 80:1062–1064.

This study reports the identification of a novel SNCA mutation and the associated clinical and pathological features.

44. Polymenopoulos MH, Lavender C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson’s disease. Science 1997; 276:2045–2047.

45. Appel-Cresswell S, Vilarino-Guell C, Encarnacion M, et al. Alpha-synuclein pH50Q, a novel pathogenic mutation for Parkinson’s disease. Mov Disord 2013; 28:811–813.

This study reports a novel H50Q SNCA mutation in a sporadic Parkinson’s disease patient.

46. Lesage S, Anheim M, Letourneur F, et al. G51D alpha-synuclein mutation causes a novel parkinsonian-pyramidal syndrome. Ann Neurol 2013. doi: 10.1002/ana.23984.

The authors report a novel G51D SNCA mutation and associated clinical and pathological features, coupled with functional studies.

47. Kara E, Lewis P, Ling H, et al. LAOAG: a novel parkinsonian-pyramidal syndrome. Neurobiol Aging 2012; 33:814–823.

48. Xiourou M, Vogiatzis T, Vekrellis K, et al. Alpha-synuclein degradation by autophagy pathways: a potential key to Parkinson’s disease pathogenesis. Autophagy 2008; 4:917–919.

49. Xiourou M, Vogiatzis T, Vekrellis K, et al. Abberant alpha-synuclein confers toxicity to neurons in part through inhibition of chaperone-mediated autophagy. PLoS One 2009; 4:e5515.

50. Cuervo AM, Stefanis L, Fredenburg R, et al. Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science 2004; 305:1292–1295.

51. Tanik SA, Schulteis CE, Volpicelli-Daley LA, et al. Lewy body-like alpha-synuclein aggregates resist degradation and impair macroautophagy. J Biol Chem 2013; 288:15194–15201.

The authors show that α-synuclein aggregates impair autophagy.

52. Choi AM, Ryter SW, Levine B. Autophagy in human health and disease. N Engl J Med 2013; 368:651–662.

This review article summarises the role of autophagy in the development of various diseases including cancer and neurodegeneration.

53. Winslow AR, Rubinsztein DC. The Parkinson disease protein alpha-synuclein inhibits autophagy. Autophagy 2011; 7:429–431.

54. Ahmed I, Luang Y, Schools S, et al. Development and characterization of a new Parkinson’s disease model resulting from impaired autophagy. J Neurosci 2012; 32:16500–16509.

This is a study on a mouse model carrying a conditional deletion in the autophagy gene atg7 that demonstrated neuropathologic features of Parkinson’s disease.

55. Park JS, Mehta P, Cooper AA, et al. Pathogenic effects of novel mutations in the P-type ATPase ATP13A2 (PARK9) cause a Kufer-Rakeb syndrome, a form of early-onset parkinsonism. Hum Mol Mutat 2011; 32:956–964.

56. Ramirez A, Heimbach A, Grundenmann J, et al. Hereditary parkinsonism with dementia is caused by mutations in ATP13A2, encoding a lysosomal type 5 P-type ATPase. Nat Genet 2006; 38:1184–1191.

57. Di Fonzo A, Chien HF, Socal M, et al. ATP13A2 missense mutations in juvenile parkinsonism and young onset Parkinson disease. Neurology 2007; 68:1557–1562.

58. Lees AJ, Singleton AB. Clinical heterogeneity of ATP13A2 linked disease (Kufer-Rakeb) justifies a PARK designation. Neurology 2007; 68:1553–1554.

59. Lin CH, Tan EK, Chen ML, et al. Novel ATP13A2 variant associated with Parkinson disease in Taiwan and Singapore. Neurology 2008; 71:1727–1729.

60. Bras J, Verloes A, Schneider SA, et al. Mutation of the parkinsonism gene ATP13A2 causes neuronal ceroid-lipofuscinosis. Hum Mol Genet 2007; 16:2685–2686.

This study reports the identification of ATP13A2 mutations as the cause of a lysosomal storage disorder in humans.

61. Wohlecke A, Philipp U, Bock P, et al. A non base pair deletion in the canine ATP13A2 gene causes seizures and late-onset neuronal ceroid lipofuscinosis in the Tibetan terrier. PLoS Genet 2011; 7:e1002304.

62. Fairna FH, Zeng R, Johnson GS, et al. A truncating mutation in ATP13A2 is responsible for adult-onset neuronal ceroid lipofuscinosis in Tibetan terriers. Neuron 2011; 12:482–474.
Movement disorders

75. Dehay B, Ramirez A, Martinez-Vicente M, et al. Loss of P-type ATPase
ATP13A2/PARK9 function induces general lysosomal deficiency and leads to Parkinson disease neurodegeneration. Proc Natl Acad Sci USA 2012; 109:9811–9816.

This study reports on the impact on lysosomal function of ATP13A2 loss of function.

76. Gitter AD, Chesi A, Geddie ML, et al. Alpha-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity. Nat Genet 2009; 41:308–315.

77. Userovici M, Tresse E, Mazzulli JR, et al. Deficiency of ATP13A2 leads to lysosomal dysfunction, alpha-synuclein accumulation, and neurotoxicity. J Neurosci 2012; 32:4240–4246.

This study investigates the impact of ATP13A2 deficiency on lysosomal function and α-synuclein homeostasis.

78. Schulteis PJ, Fleming SM, Clippinger AK, et al. ATP13a2-deficient mice exhibit neuronal ceroid lipofuscinosis, limited α-synuclein accumulation, and age-dependent sensorimotor deficits. Hum Mol Genet 2015; 24:2087–2092.

This study shows that loss of ATP13A2 results in α-synuclein accumulation and formation of lipofuscin inclusions.

79. Shachar T, Lo Bianco C, Recchia A, et al. Lysosomal storage disorders and Parkinson’s disease: Gaucher disease and beyond. Mov Disord 2011; 26:1593–1607.

80. Qiao L, Hamamichi S, Caldwell KA, et al. Alpha-synuclein cytopathic D protects against alpha-synuclein aggregation and toxicity. Mol Brain 2008; 1:17.

81. Cullen V, Lindfors M, Nj G, et al. Cathepsin D expression level affects alpha-synuclein processing, aggregation, and toxicity in vivo. Mol Brain 2009; 2:5.

82. Stevede D, Liang P, Yen SH. Cathepsin D is the main lysosomal enzyme involved in the degradation of alpha-synuclein and generation of its carboxy-terminal truncated species. Biochemistry 2008; 47:9678–9687.

83. Goudreau N, Lamsa A, Amour R, et al. Autosomal recessive parkinsonism linked to parkin gene in a Tunisian family. Clin Genet 2012; 9:247–251.

84. Hayashi S, Wababayashi K, Ishikawa A, et al. An autopsy case of autosomal-recessive juvenile parkinsonism with a homozygous exon 4 deletion in the parkin gene. Mov Disord 2010; 25:884–888.

85. Pramstaller PP, Schlossmacher MG, Jacques TS, et al. Parkinson’s disease: pathology, pathogenesis, and treatment. Mov Disord 2009; 24:197–211.

86. Kordower JH, Choi Y, Hauser RA, et al. Lewy body pathology in long-term embryonic nigral transplants in Parkinson’s disease. Nat Med 2008; 14:504–506.

87. Lebouvier T, Neunlist M, Bruyé des Varannes S, et al. Colonic biopsies to assess the neuropathology of Parkinson’s disease and its relationship with symptoms. PLoS One 2010; 5:e12728.

88. Li JY, Englund E, Holton JL, et al. Lewy body pathology in subjects with Parkinson’s disease suggest host-to-graft disease propagation. Nat Med 2008; 14:501–503.

89. Ahn TB, Langston JW, Aachi VR, Dickson DW. Relationship of tissue and global α-synuclein pathology in a fetal transplant for Parkinson’s disease. Am J Pathol 2012; 14:501–503.

This study examines the relation of α-synuclein pathology to glosis in a fetal graft in a Parkinson’s disease patient.

90. Nordemeyer K, Prakash H, Meitinger T. An isoform of HPAK2, deficient in parkinopathy-associated neurodegeneration, localizes to mitochondria. Hum Mol Genet 2003; 12:321–327.

91. Alfonso-Pecchio A, Garofoli MC, Leventis R, Jackowski S. Compartmentalization of mammalian pantetheine kinases. PLoS One 2012; 7:e49509.

This study indicates that missfolded α-synuclein can be transmitted between brain regions.

92. Luk KC, Kehm V, Carroll J, et al. Pathological α-synuclein transmission stimulates Parkinson-like neurodegeneration in nontransgenic mice. Science 2012; 339:949–953.

This study provides supporting evidence for the contribution of the disease spread hypothesis of α-synuclein to Parkinson’s disease pathogenesis.

93. Mougenot AL, Nicot S, Bencsik A, et al. Prion-like acceleration of a synucleinopathy in a transgenic mouse model. Neurobiol Aging 2011; 32:2225–2228.

94. Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson’s disease. Neurobiol Aging 2003; 24:197–211.

95. Lebouvier T, Neunlist M, Bruyé des Varannes S, et al. Colonic biopsies to assess the neuropathology of Parkinson’s disease and its relationship with symptoms. PLoS One 2010; 5:e12728.

96. Li JY, Englund E, Holton JL, et al. Lewy body pathology in subjects with Parkinson’s disease suggest host-to-graft disease propagation. Nat Med 2008; 14:501–503.

97. Ahn TB, Langston JW, Aachi VR, Dickson DW. Relationship of tissue and global α-synuclein pathology in a fetal transplant for Parkinson’s disease. Am J Pathol 2012; 14:501–503.

This study examines the relation of α-synuclein pathology to glosis in a fetal graft in a Parkinson’s disease patient.

98. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.

99. Russo I, Babacou L, Gregorio E. Exomes-associated neurodegeneration and progression of Parkinson’s disease. J Neurol Neurosurg Psychiatry 2012; 83:127–132.

This study reports on the kinetics of α-synuclein fibril formation.

100. Desplats P, Lee HJ, Bae EJ, et al. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of α-synuclein. Proc Natl Acad Sci USA 2006; 103:13010–13015.

101. Carmen C, Angot E, Bergstrom AL, et al. Prion-like acceleration of a synucleinopathy in a transgenic mouse model. Neurobiol Aging 2011; 32:2225–2228.

102. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.

103. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.

104. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.

105. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.

106. Vekrellis K, Xlouris M, Emmanoulidou E, et al. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol 2011; 10:1015–1025.
et al. Form a multiprotein complex with Miro and Milton, linking PINK1 function to mitochondrial trafficking. Biochimie 2009; 91:2045–2052.

134. Liu S, Sawada T, Lee S, et al. Parkinson’s disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS Genet 2012; 8:e1002537.

This study shows that PINK1 regulates mitochondrial trafficking through Miro.

135. Ding WX, Guo F, Ni HM, et al. Parkinson and mitofusins reciprocally regulate mitochondrial andochondroplasia. J Biol Chem 2012; 287:42379–42388.

This study reports that loss of parkin induces the formation of neuroaxonal spheroids.

136. Nissen PC, Bruse E, Leyten AC, et al. Autosomal dominant adult neuronal ceroid lipofuscinosis: parkinsonism due to both striatal and nigral dysfunction. Mov Disord 2002; 17:482–487.

137. Taybi N, Walker J, Stubblefield B, et al. Gaucher disease with parkinsonian manifestations: does glucocerebrosidase deficiency contribute to a vulnerability to parkinsonism? Mol Genet Metab 2003; 79:104–109.

138. Goker-Alpan O, Schiffmann R, LaMarca ME, et al. Parkinsonism among Gaucher disease carriers. J Med Genet 2004; 41:937–940.

139. Tan EM, Ho P, Tan L, et al. PLA2G6 mutations and Parkinson’s disease. Ann Neurol 2004; 56:149–156.

140. Tofaris GK. Lysosome-dependent pathways as a unifying theme in Parkinson’s disease. Mov Disord 2012; 27:1364–1369.

This review summarizes the role of lysosomal pathways in the pathogenesis of Parkinson’s disease.

141. Morgan NW, Westaway SK, Morton JE, et al. PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. Hum Genet 2006; 120:752–754.

142. Wild P, Dicky I. Mitochondria get a Parkin’ ticket. Nat Cell Biol 2010; 12:104–106.

143. Geisler S, Holmstrom KM, Treis A, et al. The PINK1/Parkin-mediated mitophagy is compromised by PD-associated mutations. Autophagy 2010; 6:871–878.

144. Geisler S, Holmstrom KM, Skujat D, et al. PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol 2010; 12:119–131.

145. Poole AC, Thomas RE, Andrews LA, et al. The PINK1/Parkin pathway regulates mitochondrial morphology. Proc Natl Acad Sci USA 2008; 105:1638–1643.

146. Narendran D, Tanaka A, Suen DF, Youle RJ. Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. J Cell Biol 2008; 183:795–803.

147. Vives-Bauza C, Zou C, Huang Y, et al. PINK1-dependent recruitment of Parkin to damaged mitochondria in mitochondria. Proc Natl Acad Sci USA 2010; 107:378–383.

148. Vives-Bauza C, Przedborski S. PINK1 points to Parkin to mitochondria. Autophagy 2010; 6:674–675.

149. Vives-Bauza C, de Vries RL, Tocilescu M, Przedborski S. PINK1/Parkin direct mitophagy to damaged mitochondria. Autophagy 2010; 6:315–316.

150. Haskin J, Sargar R, Shani V, et al. AF-6 is a positive modulator of the PINK1/ Parkin pathway and is deficient in Parkinson’s disease. Hum Mol Genet 2013; 22:2083–2096.

This study identifies AF-6 as a recruiter of parkin to mitochondria with a possible role in Parkinson’s disease.

151. Okatsu K, Oka T, Iuchi M, et al. PINK1 autophosphorylation upon membrane potential dissipation is essential for Parkin recruitment to damaged mitochondria. Nat Commun 2012; 3:1016.

This study shows that autophosphorylation of PINK1 precedes the recruitment of parkin to mitochondria.

152. Matsui H, Gavino R, Asano T, et al. PINK1 and Parkin complementarily protect dopaminergic neurons in vertebrates. Hum Mol Genet 2013; 22:2423–2434.

This study emphasizes the synergistic role of parkin and PINK1 in mitochondrial physiology.

153. Dehay B, Martinez-Vicente M, Caldwell GA, et al. Lysosomal impairment in Parkinson’s disease. Mov Disord 2013; 28:725–732.

This review article summarises the involvement of lysosomal pathways in the pathogenesis of Parkinson’s disease.

154. Gar-On Z, Ozelius LJ, Bar-Shira A, et al. The PL302P mutation in the lysosomal enzyme gene SMPD1 is a risk factor for Parkinson disease. Neurology 2013; 81:1854–1861.

This study provides preliminary evidence that a variant in SMPD1 increases the risk for the development of Parkinson’s disease in the Ashkenazi Jews.

155. Imaizumi Y, Okada Y, Akamatsu W, et al. Mitochondrial dysfunction associated with increased oxidative stress and alpha-synuclein accumulation in PARK2 iPSC-derived neurons and postmortem brain tissue. Mol Brain 2012; 5:35.

This is a study on neurons derived from iPS cells from carriers of parkin mutations reproducing the neuropathological findings in these patients.

156. Sarraf SA, Raman M, Guarnier-Pereira V, et al. Landscape of the PARKIN-dependent ubiquilome in response to mitochondrial depolarization. Nature 2013; 496:372–376.

In this study, the authors carried out a high throughput study in order to identify the ubiquilination targets of parkin.

157. Malik I, Turk J, Marcuso DJ, et al. Disrupted membrane homeostasis and accumulation of ubiquitinated proteins in a mouse model of infantile neuronal-axonal dysfunction caused by PLA2G6 mutations. Am J Pathol 2008; 172:406–416.

158. Grunwald A, Ames B, Seibler P, et al. ATP13A2 mutations impair mitochondrial function in fibroblasts from patients with Kufor-Rakeb syndrome. Neurol Aging 2012; 33:1843–e1841–e1847.

This is the first functional study on fibroblasts from patients with ATP13A2 mutations and shows that mitochondrial function is impaired in carriers of mutations in a lysosomal protein.

159. Urichich A, Benet-Pages A, Strahl W, et al. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am J Hum Genet 2011; 89:168–175.

160. Valimori-Guell C, Wider C, Rivas OA, et al. VPS35 mutations in Parkinson disease. Am J Hum Genet 2011; 89:162–167.

161. Bi F, Li F, Huang C, Zhou H. Pathogenic mutation in VPS35 impairs its protection against MPP(+) cytotoxicity. Int J Biol Sci 2013; 9:149–155.

This study shows that VPS35 mutations can impair mitochondrial function.

162. Wider C, Skipper L, Solida A, et al. Autosomal dominant dopa-responsive parkinsonism in a multigenerational Swiss family. Parkinsonism Relat Disord 2008; 14:465–470.

163. Gomez-Suaga P, Luzon-Toro B, Churamani D, et al. Leucine-rich repeat kinase 2 regulates autophagy through a calcium-dependent pathway involving NAADP. Hum Mol Genet 2012; 21:511–525.

This study shows that LRRK2 could have a role in autophagy and indicates a mechanism underlying this relation.

164. Orenstein SJ, Kuo SH, Tasset I, et al. Interplay of LRRK2 with chaperone-mediated autophagy. Nat Neurosci 2013; 16:394–406.

This study reports that LRRK2 mutations can inhibit autophagy potentially affecting degradation of u-synuclein.

165. Yue Z, Yang XW. Dangerous dust: LRRK2 and alpha-synuclein jam at CMA. Nat Neurosci 2013; 16:375–377.

This study evaluates the findings of Orenstein et al. (2013).

166. Maclaurin DA, Rhinn H, Kwahara T, et al. RAB7L1 in which a haplotype increasing the risk for Parkinson’s disease was identified GWA studies.

167. 1350-7540 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins www.co-neurology.com 393
Movement disorders

169. Mortiboys H, Johansen KK, Aasly JO, Bandmann O. Mitochondrial impairment in patients with Parkinson disease with the G2019S mutation in LRRK2. Neurology 2010; 75:2017–2020.

170. Hindle S, Afsoon F, Stark M, et al. Dopaminergic expression of the Parkin- nian gene LRRK2-G2019S leads to nonautonomous visual neuroderegenera- tion, accelerated by increased neural demands for energy. Hum Mol Genet 2013; 22:2129–2140. This study reports on a large cohort study of VPS35.

171. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal- dominant parkinsonism with pleomorphic pathology, Neuron 2004; 44:601– 607.

172. Duran R, Mencacci NE, Angeli AV, et al. The glucocerebrosidase E326K variant predisposes to Parkinson’s disease, but does not cause Gaucher’s disease. Mov Disord 2012; 28:232–239.

173. Song W, Wang F, Savin M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet 2013; 22:1994–2009.

174. Dementzaki G, Dimitriou E, Kloum M, et al. Loss of beta-glucocerebrosidase activity does not affect alpha-synuclein levels or lysosomal function in neuronal cells. PloS One 2013; 8:e60674.

175. This study investigates the effect of SNCA on mitochondria. The glucocerebrosidase E326K variant predisposes to Parkinson’s disease, but does not cause Gaucher’s disease. Mov Disord 2012; 28:232–239.

176. This study shows that the E362K GBA variant causes Parkinson’s disease but never Gaucher’s disease suggesting a possible disassociation between the pathogenetic mechanisms of the two diseases.

177. Song W, Wang F, Savin M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet 2013; 22:1994–2009.

178. This study identifies the rare MAPT p.A152T variant in patients with parkinsonism with tubulin influences on the polymerization of microtubule in vitro and structure of microtubule in cells. Mol Biol Reports 2010; 37:3183–3192.

179. This study describes the effect of SNCA on mitochondria. The glucocerebrosidase E326K variant predisposes to Parkinson’s disease, but does not cause Gaucher’s disease. Mov Disord 2012; 28:232–239.

180. This study shows that the E362K GBA variant causes Parkinson’s disease but never Gaucher’s disease suggesting a possible disassociation between the pathogenetic mechanisms of the two diseases.

181. Cali T, Ottoni D, Negro A, Bini M. alpha-Synuclein controls mitochondrial calcium homeostasis by enhancing endoplasmic reticulum-mitochondria interactions. J Biol Chem 2012; 287:17914–17929.

182. This study reports TFEB as a regulator of GBA within the lysosomes.

183. Dementzaki G, Dimitriou E, Kloum M, et al. Loss of beta-glucocerebrosidase activity does not affect alpha-synuclein levels or lysosomal function in neuronal cells. PloS One 2013; 8:e60674.

184. This study shows that the E362K GBA variant causes Parkinson’s disease but never Gaucher’s disease suggesting a possible disassociation between the pathogenetic mechanisms of the two diseases.

185. Song W, Wang F, Savin M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet 2013; 22:1994–2009.

186. This study reports TFEB as a regulator of GBA within the lysosomes.

187. This study shows that the E362K GBA variant causes Parkinson’s disease but never Gaucher’s disease suggesting a possible disassociation between the pathogenetic mechanisms of the two diseases.

188. This study identifies the rare MAPT p.A152T variant in patients with parkinsonism with tubulin influences on the polymerization of microtubule in vitro and structure of microtubule in cells. Mol Biol Reports 2010; 37:3183–3192.

189. This study describes the effect of SNCA on mitochondria. The glucocerebrosidase E326K variant predisposes to Parkinson’s disease, but does not cause Gaucher’s disease. Mov Disord 2012; 28:232–239.

190. This study identifies the rare MAPT p.A152T variant in patients with parkinsonism with tubulin influences on the polymerization of microtubule in vitro and structure of microtubule in cells. Mol Biol Reports 2010; 37:3183–3192.

191. This study shows that the E362K GBA variant causes Parkinson’s disease but never Gaucher’s disease suggesting a possible disassociation between the pathogenetic mechanisms of the two diseases.

192. Song W, Wang F, Savin M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet 2013; 22:1994–2009.

193. This study identifies the rare MAPT p.A152T variant in patients with parkinsonism with tubulin influences on the polymerization of microtubule in vitro and structure of microtubule in cells. Mol Biol Reports 2010; 37:3183–3192.

194. This study describes the effect of SNCA on mitochondria. The glucocerebrosidase E326K variant predisposes to Parkinson’s disease, but does not cause Gaucher’s disease. Mov Disord 2012; 28:232–239.

195. Song W, Wang F, Savin M, et al. TFEB regulates lysosomal proteostasis. Hum Mol Genet 2013; 22:1994–2009.