Pathogenic Mechanisms of Neurodegeneration in Parkinson Disease

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KEYWORDS
- Parkinson disease • α-Synuclein • Lewy bodies • Mitochondrial dysfunction

KEY POINTS
- Sporadic Parkinson disease (PD) represents an accelerated extreme of the normal spectrum of human senescence.
- Recent discoveries have shown that it is likely to result from the effect of many small but quantifiable genetic risk factors, in combination possibly with the effect of certain environmental insults.
- α-Synuclein is the presynaptic protein that constitutes the principal component of Lewy bodies, the pathologic hallmark of PD. Its transformation to fibrillar and oligomeric forms appears to be the key to its neuronal toxicity.
- Although its exact role in the etiology of sporadic PD is unclear, mitochondrial dysfunction appears to play a major role in its pathogenesis.
- The basis for the selective toxicity to dopaminergic cells that characterizes PD remains unclear.

HISTOLOGY, EPIDEMIOLOGY AND GENETICS OF SPORADIC PARKINSON DISEASE

Lewy bodies (LB), discovered in 1912 by Frederic Lewy, remain the pathologic hallmark of Parkinson disease (PD). Their distribution is thought to follow a sequential appearance within the dorsal motor nucleus, olfactory bulbs and nucleus, locus ceruleus, and subsequently, in the substantia nigra pars compacta (SNc). Neuronal cell loss in PD appears first in the dopaminergic cells of the SNc. It has been estimated that dopamine levels in the striatum are reduced to approximately 60% to 70% of normal values at the time of diagnosis. Degeneration of non-dopaminergic neurons...
also occurs in PD, but usually later in the course of the disease. The cholinergic nucleus basalis of Meynert, the serotoninergic neurons of the raphe nucleus, and the hypocretin-containing neurons of the hypothalamus suffer neuron loss with advanced disease.1

Consistently, age is the greatest risk factor for sporadic PD.2,3 In the United States, the age-adjusted incidence is 13.5 to 13.9 per 100,000 person-years.2,4 Age-adjusted prevalence is approximately 115 per 100,000, estimated as 1.3 per 100,000 under age 45 years, and 1192.9 per 100,000 in patients aged 75 to 85 years.5 Conversely, a prevalence study in Holland found 3100 cases per 100,000 aged 75 to 85 years and 4300 per 100,000 for those older than 85 years.5 The pathological progression of PD occurs in advance of symptomatic motor PD, with the so-called premotor symptoms, including rapid eye movement sleep disturbance, constipation, subcortical cognitive impairment, and hyposmia potentially preceding it by decades.6 Imaging with positron emission tomography (PET) suggests the preclinical period of cell loss within the SNc is around 8 years, with the greatest rate of decline in the early stages of the disease.7 LB have been found within the brains of normal aged subjects,8,9 perhaps the best indication that PD as a disease entity should be viewed as the accelerated extreme of the “normal” spectrum of senescence. Conversely, in dementia with LB, Lewy pathology with an extremely similar distribution to that in advanced PD10 leads to a progressive subcortical dementia with or without Parkinsonism,11 highlighting the variable penetrance of the motor PD phenotype and Lewy pathology’s lack of specificity to it.

Although caution must be exercised when correlating the histological stigmata of PD with its clinical and, specifically, its motor signs, the PD phenotype remains remarkably robust. Genome-wide association studies (GWAS) correlate single-nucleotide polymorphisms (SNPs) within the genomes of disease carrying subjects and compare them to controls to calculate (expressed as an odds ratio) the risk associated with those SNPs.12 The success of GWAS in the context of the PD phenotype attests to its specificity. GWAS studies have confirmed the importance of several gene loci, associated with mendelian forms of PD13,14 (see later discussion). With the exception of LRRK2, truly mendelian pathogenic mutations are comparatively rare. However, haplotypes within the same gene loci confer a smaller PD risk with a much greater frequency. In addition, SNPs in novel loci, not previously associated with PD risk, have been identified and confirmed as risk factors for PD.14 The most prominent example is the consistent recording of the microtubule associated protein τ (MAPT), more commonly associated with the pathogenesis of Alzheimer disease, as a major risk allele locus for PD, the implications of which on the established LB centric model of PD remain unclear.

Age and genetic predispositions aside, other environmental factors have been proposed as risk associations in the pathogenesis of sporadic PD. Consistently, chronic tobacco smoke inhalation and coffee drinking have been shown to reduce the risk for PD. In the case of the former, the relationship appears to be dose-dependent and occurs even when the added burden of mortality from the complications of smoking are taken into account.15 Pesticide exposure, rural living, and farming seem to confer an increased risk of the development of PD, although it is not clear whether farming represents a confounding association with pesticide exposure.16 Nonsteroidal anti-inflammatory drug exposure, traumatic brain injury, and several other environmental risk factors17 have also been identified as contributory; however, the odds ratios (ORs) of any of these risks are not sufficient to cause PD in isolation. Their role in the pathogenesis of PD therefore seems likely to be small, probably in conjunction with a (or a combination of) predisposing genetic risk factor(s).
An as yet underdeveloped field which almost certainly makes a significant contribution to PD risk is that of epigenetics. Epigenetic modifications provide phenotypic plasticity, allowing adaptation to a change in the environment without modifying the genotype. Hence, through processes such as methylation, phosphorylation, acetylation, and generation of micro-RNAs (miRNA), expression of genes can be modulated in response to environmental stimuli. Although the field is in its infancy, there are promising signs that it may yield fruitful insights into potentially modifiable epigenetic processes contributing to PD pathogenesis. There is, for instance, evidence that epigenetic methylation of the \( \alpha \)-synuclein (SNCA) locus upregulates its translation, with methylation levels being reduced in the substantia nigra of sporadic PD brains. Similarly, sporadic PD patients have been shown to have differential expression of various miRNA probes, including miR-34b/c, which has been associated with the development mitochondrial dysfunction.

\( \alpha \)-SYNUCLEIN

The first indication of the significance of the presynaptic protein SNCA in the pathogenesis of PD came with the discovery of the A53T mutation of the SNCA gene, which gives rise to an autosomal-dominant form of familial PD in the fifth to sixth decade. Subsequently, SNCA was discovered to be the principal component of LB. Further autosomal-dominant mutations at E46K and A30P leading to PD in the third to fifth and fifth to seventh decade, respectively, were identified along with, more recently, two putative pathogenic substitutions at H50Q and G51D. In vitro work subsequently revealed that heterozygous A53T and A30P transgenic mice develop certain aspects of the motor and histological PD phenotype.

The next breakthrough came with the discovery that SNCA gene triplications and subsequent duplications led to PD in a dose-dependent manner. A family with an autosomal-dominant form of PD with onset in the fourth decade was found to have a triplication in the SNCA gene, while subjects with a duplication were found to develop PD from the fifth decade, with relative SNCA expression levels being in proportion to the gene copy number “dosage.” GWAS have shown that overexpression of SNCA mediated by the Rep1 promoter region confers an increased risk of sporadic PD. The SNCA locus is consistently the most frequent association in GWAS quantifying the risk of PD associated with SNPs.

Despite SNCA’s evident significance to the pathogenesis of PD, the pressing question of its physiological function remains unsolved. Pertinently, homozygous SNCA knockout mice do not display a Parkinsonian phenotype, although some groups report mild impairment to vesicle trafficking and dopamine release. SNCA is predominately a presynaptic terminal protein associated with the distal synaptic reserve. Knockdown or depletion of SNCA in transgenic mice and primary hippocampal neurons deplete synaptic vesicles and impair their mobilization to the presynaptic terminus, although intriguingly it seems to be a viable phenotype.

SNCA’s conformational properties appear to be a key factor in its pathogenicity. It exists as a monomer in its native state, but has a propensity to defer to a \( \beta \)-sheet-rich amyloid aggregate following, among other factors, oxidative stress, post translational modification, or contact with lipids. Oligomeric then protofibrillar intermediaries are precursors to this aggregated form, and it is this transition and these conformations that are thought to confer toxicity. This theme is borne out in the finding that familial mutations of SNCA have faster (A53T, E46K, H50Q) or slower (A30P) aggregation compared with wild type and that within LBs SNCA is predominately in its fibrillar and aggregated forms.
SNCA’s conformational properties have been further brought into focus by the unexpected finding that it may exhibit “prion-like” properties. Prions are aberrantly folded “infectious” proteins, which, in the absence of nucleic acids, propagate their misfolded β-sheet-rich and aggregated structure to the adjacent native state proteins. The relevance of these proteins to the pathogenesis of PD was sparked by the finding that healthy neurons implanted into PD brains (as part of a therapeutic trial) developed LBs some eleven to sixteen years later pathology which was present 16 months following transplantation. Subsequently, it was shown in a variety of models that SNCA can enter the cell via endocytosis, interact directly with and propagate through adjacent cells. This aggregated and “transplanted” SNCA from “infected” cells was able to induce aggregation of host SNCA. The same study was able to show in vivo transfer of misfolded SNCA to grafted neurons in the striatum of mice overexpressing SNCA, findings that were replicated in the striatum of rats. Similarly preformed fibrils of SNCA injected directly into the striatum of mice have been shown to result in progressive Lewy-derived neuronal toxicity in anatomically adjacent areas. In this study, a progressive reduction of dopamine concentration and impaired motor performance were noted in comparison with mice injected with phosphate-buffered saline, pathology that could be partially rescued with knock-out of the SNCA gene. These studies provide some correlation with Braak’s clinical and histopathological observation that Lewy pathology spreads consecutively from the first, ninth, and tenth cranial nerves/nuclei through the brainstem, cortex, and on to the neocortex. Accordingly, the “seeding” observed in vitro and in vivo may be analogous to the progression of LBs in humans, with SNCA aggregation “transmitted” from these selectively vulnerable cranial nerve structures.

There is evidence that SNCA may compromise autophagic cellular degradation mechanisms. Autophagy, which broadly speaking degrades long-lived intracellular proteins, comprises 3 mechanisms: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA). In macroautophagy, double-membraned autophagosomes fuse with lysosomes to deliver cytoplasmic contents, including misfolded or aggregated proteins for digestion, while microautophagy delivers the same outcome by lysosomal pinocytosis of cytoplasmic contents. CMA depends on the protein chaperone hsc70 and its binding to LAMP-2A, a lysosomal surface receptor. A highly specific subset of cytosolic proteins with a KFREQ motif is recognized by the hsc70 chaperone and internalized for degradation by LAMP-2A lysosomal membrane receptors. There is abnormal expression of lysosomal proteins in the substantia nigra of PD brains, implying activation of lysosomal pathways common to all 3 autophagial mechanisms. More specifically, SNCA’s pentapeptide sequence is consistent with LAMP-2A binding and in lysosomal preparations of SNCA have been shown to be degraded following binding to it. In this system, mutant SNCA was bound to this lysosomal receptor with high affinity but was not translocated across the membrane and appeared to block these receptors, thereby inhibiting the CMA pathway, suggesting mutant SNCA may differentially accumulate through CMA inhibition by SNCA mutants. Macroautophagic inhibition with bafilomycin has been shown to cause accumulation of mutant SNCA; conversely, macroautophagial enhancement with rapamycin accelerates clearance of both wild type and mutant SNCA. Overexpression of beclin 1 (another macroautophagial inducer) was able to reduce SNCA levels in mouse brains, providing in vitro correlation of macroautophagy’s involvement in SNCA clearance SNCA. Moreover, the proteosomal system, which is responsible for the removal of short-lived proteins, has also been implicated in SNCA degradation, although its exact role is controversial. It has been reported that oligomeric SNCA is targeted to the 26S
subunit of the proteasome, which, in the process of trying to degrade the protein, is functionally inhibited by it. Conversely, 26S depletion in mice causes early neurodegeneration and striatal accumulation of SNCA. There is at present no consensus as to the significance of these findings, or indeed, what the exact role of the lysosomal and proteosomal degradation of SNCA in PD is. It may be that SNCA’s degradation pathway is determined by its conformational state, with monomeric and smaller oligomeric species being degraded by proteosomal and CMA pathways, while larger fibrillar and aggregated forms require bulk disposal with macroautophagy. What is clear is that protein degradation pathways represent a promising area for therapeutic innovation, with upregulation potentially providing an accessible means of removing toxic oligomeric and fibrillar SNCA from the brain.

GLUCOCEREBROSIDASE

The role of glucocerebrosidase (GBA) in the pathogenesis of PD has begun to come to prominence in recent years. GBA is a lysosomal hydrolase, which, through β-cleavage of the β-glucosidic linkage, degrades glucosylceramide to ceramide within the lysosome. Mutations in GBA lead to the autosomal-recessive condition Gaucher disease, a lysosomal storage disorder, common among Ashkenazi Jews, resulting in glucosylceramide accumulation in visceral organs and a variety of clinical phenotypes. A decade ago, it was observed that a higher proportion of Gaucher’s patients developed motor features of PD and subsequently that there was a higher incidence of PD among the pedigree of homozygous mutation carriers, many of whom were obligate heterozygotes. Conversely, it was found that heterozygous carriers of GBA mutants had a variable penetrance of the PD phenotype. In turn, compared with controls, heterozygous Gaucher’s patients were found to have a combined odds ratio (OR) of 5.43 of developing PD, with the N370S mutation having an OR of 3.51 based on a candidate gene approach in a GWAS meta-analysis. Recent data suggest that heterozygote states confer a cumulative risk of developing PD of 5% at age 60 rising to 15% at age 80. Numerically, GBA is now the greatest genetic risk factor for PD, with mutation prevalence estimated between 2.3% and 9.4% in non-Ashkenazi PD populations.

Intriguingly, there appears to be evidence of an interaction between GBA and SNCA. Analysis of postmortem brains of sporadic PD patients without GBA mutations showed reduced levels of GBA activity, while several studies have demonstrated that inhibition or knockdown of GBA causes accumulation of SNCA in cell lines expressing pathogenic PD mutations. Conversely, overexpression of SNCA leads to reduced GBA activity. Such an interaction could explain the limited penetrance of parkinsonism in heterozygous Gaucher carriers, with the “priming” effect of a predisposition to SNCA aggregation bringing out the pathogenicity of the GBA mutant.

Evidence for the dysfunctional autophagic disposal of SNCA has already been outlined above; however, an important and developing strand of thinking relating to the pathogenicity of mutant GBA is that it acts to impair SNCA autophagy. A recent study found evidence of increased autophagic markers in GBA homozygous knockout primary neuronal culture, while another demonstrated that impaired GBA activity contributed to reduced lysosomal activity. The same study also indicated that GBA mutations promote the aggregation to and stabilization of oligomeric SNCA species and, conversely, that SNCA overexpression causes GBA to be sequestered within the endoplasmic reticulum (ER), leading to an increase in reactive oxygen species production and cellular stress. Encouragingly, treatment of disease-carrying fibroblasts and neuroblastoma cells with the ambroxol, a pH-dependent mixed type
inhibitor of GBA, appears to restore GBA activity and reduce SNCA expression in GBA cell lines.\textsuperscript{86,87} It has been postulated that this occurs by correction of aberrant GBA folding, facilitating trafficking of GBA through the ER.\textsuperscript{88}

**LEUCINE-RICH REPEAT KINASE 2**

An autosomal-dominant form of PD commonly presenting in the sixth decade caused by a mutation in Leucine-rich repeat kinase 2 (\textit{LRRK2}) was first identified in a Japanese family in 2002,\textsuperscript{89} with further kindreds identified in the subsequent years,\textsuperscript{90,91} including, in 2005, G2019S, the most common mutation.\textsuperscript{92} Although there is widespread variation in mutation frequency dependent on ethnicity, it is clear that \textit{LRRK2} is a common mutation that exhibits incomplete penetrance, with the PD phenotype emerging in an age-dependent fashion.\textsuperscript{93} In the case of G2019S, for instance, between 0.5% and 12.4% of familial and 0.1% to 4.3% of sporadic Caucasian PD cases carry the mutation, while figures as high as 43% and 33%, respectively, have been recorded in Arabic populations.\textsuperscript{94}

\textit{LRRK2} is a cytosolic protein of unknown function that has been implicated in a variety of roles, including neurite growth, cytoskeleton maintenance, vesicle trafficking, and autophagy.\textsuperscript{46,95–98} It contains a kinase and a GTPase domain; however, at present, its substrate is unknown. As well as the PD phenotype, mutants have been implicated in the pathogenesis of inflammatory bowel disease,\textsuperscript{99} a variety of cancers, and leprosy.\textsuperscript{100} It can display a more heterogeneous pathologic picture than other forms of PD, with tau, neurofibrillary tangles, and anterior horn cell pathology occasionally described with or without LB and nigrostriatal degeneration.\textsuperscript{101–104} Apart from its high-allele frequency, of particular interest is its apparent characteristic to exhibit pathogenicity in a gain of function-dependent manner, whereby pharmacological kinase inhibition appears to stabilize neuronal cell death in \textit{LRRK2} cell lines\textsuperscript{105,106} and presents a tantalizing therapeutic target, although to date, efforts to produce a viable disease-modifying kinase inhibitor have been disappointing.

**MITOCHONDRIA IN PARKINSON DISEASE**

Mitochondrial dysfunction is recognized as a pathway in the pathogenesis of PD.\textsuperscript{107} The scientific community was first alerted to the potential role of mitochondria in PD by discovery of levodopa-responsive parkinsonism following intravenous injection by drug addicts in California of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a potent inhibitor of complex I of the mitochondrial respiratory chain. Primates who were administered MPTP were found to develop clinical and pathological features of PD,\textsuperscript{108,109} and mice were found to develop dopamine depletion in the substantia nigra.\textsuperscript{110} Epidemiologic and in vitro work subsequently implicated rotenone, another complex I inhibitor, in the etiology of PD.\textsuperscript{110–112} Analysis of platelets in postmortem PD brains has revealed mitochondrial complex I inhibition in the SNc.\textsuperscript{113}

Further evidence of the role of mitochondria in PD came with the discovery that disruption of the mechanisms underlying mitochondria quality control cause PD. Mitochondria are controlled and regulated both endogenously (by the genes of mitochondria’s own DNA, mtDNA) and exogenously (by those within the nuclear DNA, nDNA) of the host cell. Quality control and exchange of mtDNA within the mitochondrial pool are accomplished by a constant and dynamic process of fission, fusion, and autophagic destruction (mitophagy). The autosomal-recessive nuclear mutations \textit{PINK1} and \textit{PAR-KIN} lead to PD onset in the fourth\textsuperscript{114,115} and third decades, respectively.\textsuperscript{116,117} Defective mitochondria are marked for destruction by the externalization to the outer mitochondrial membrane protein by PINK1, which allows recruitment and subsequent
ubiquitylation by PARKIN of external mitochondrial proteins, earmarking it for destruction by autophagic machinery. In addition to PINK1 and PARKIN, morphological and bioenergetic mitochondrial dysfunction has been described in a significant number of mutations implicated in mendelian and sporadic PD, implying that mitochondrial damage may be the downstream consequence of these functionally distinct pathogenic mechanisms.

Conversely, parkinsonism has been reported as a component of maternally inherited mitochondrial disease. The pathogenesis of these conditions is a consequence of specific inherited mutations of maternal mtDNA, resulting in clonal expansion and the presence of the mutation within all host mitochondria. These homoplasmic mutations are in contrast to those with a heteroplasmic origin, whereby spontaneous point mutations, which subsequently become clonally expanded, accumulate in a portion of host mitochondria. Specific pathogenic homoplasmic point mutations or the cumulative burden of heteroplasmic mutations past a critical threshold cause disruption of oxidative phosphorylation and hence ATP production, leading to impaired energy supply and ultimately increased susceptibility to cellular death. Heteroplasmic mutations have been recognized as a key component of human senescence, with mtDNA mutation load closely correlates with age, an observation which, given the striking age dependence of sporadic PD, has alerted many researchers to mitochondrial heteroplasmy’s possible role in its pathogenesis. An increased mutation burden was found in Parkinsonian brains at postmortem, while variation in mitochondrial haplotype (where evolutionarily conserved homoplasmic mutations in mtDNA are shared in subjects of the same or similar ethnicity) has been found to correlate with increased or decreased risk of sporadic PD. Interestingly, reports have emerged of an unexpectedly high number of HIV patients with prolonged exposure to nucleoside reverse transcriptase inhibitors (which cause a prematurely high level of mtDNA heteroplasmy), developing PD at a comparatively young age, although as yet the association remains unproven. Moreover, mutations in the polymerase $\gamma$1 ($Polg1$), a nuclear protein that acts as a “proof reading” mechanism for mitochondrial DNA, leads to Parkinsonism. Some reports have suggested variation in $Polg1$ may also be a risk factor for sporadic PD, although results are contradictory. Accordingly, mutation load within mtDNA appears to play a role in PD etiology, although the precise understanding of it remains unclear.

The predominately cytosolic protein SNCA associates with both the inner and the outer mitochondrial membranes. Overexpressed or A53T SNCA cause morphological and functional disruption of mitochondria and inhibition of complex I, while SNCA concentration within the mitochondria appears to directly correlate with the degree of complex I inhibition. Thus, there is evidence of an interaction between SNCA and mitochondria; however, its details and, more pertinently, its bioenergetic consequences remain poorly understood.

**SELECTIVE VULNERABILITY OF DOPAMINERGIC NEURONS IN PARKINSON DISEASE**

An as yet unresolved question is why the neuronal toxicity is PD is predominately confined to dopaminergic cells of the SNc. Initial attention was focused on whether this selective toxicity was a property of dopamine itself. Dopamine has been found to induce cell toxicity in the presence of SNCA that was not produced with SNCA in isolation and has been shown induce aggregation of SNCA in vitro, this has led to speculation that the oxidation of cytosolic dopamine and the free radical production it generates increases cellular stress and in turn leads to neuronal...
degeneration. If this were the case, then treatment of PD with L-3,4-dihydroxyphenylalanine (L-dopa) would be expected to accelerate the course of the disease; however, this remains an open question. In one large study, for instance, it was shown that L-dopa may slow the rate of clinical PD progression; however, conversely, single-photon emission CT brain imaging revealed reduced dopamine uptake, implying a decline in dopamine transporter integrity (hence, reduced dopamine levels). This model fails to explain why PD involves a minority of nondopaminergic neurons and equally why many dopaminergic neurons outside the SNc are spared in PD.

More recently, attention has focused on the intrinsic physiological pacemaking properties of neurons within the SNc and other parts of the mesencephalon and brainstem. This activity, essential in the case of the dopaminergic cells of the SNc for maintenance of basal dopamine levels (and hence movement), requires rapid spontaneous firing of neurons, which are highly dependent on transmembrane calcium currents. It is suggested that these currents make mitochondria particularly prone to damage, possibly by way of these neurons’ characteristic inability to buffer such calcium flux. A promising extension of this line of enquiry is the epidemiologic finding that the use of dihydropyridines, commonly used antihypertensives that antagonize L-type calcium channels, seems to exhibit a protective effect against PD. A theoretically attractive hypothesis is that blocking of these channels limits pathologic calcium flux, reducing neuronal toxicity during periods of enhanced energy demand, slowing the progression of PD.

SUMMARY

The principal impediment to progress in the understanding of PD has been the complexity of its etiology. What is certain is that a condition that was once viewed as the prototypical sporadic disease is heavily influenced by the genetic predispositions to it. The presence of toxic oligomeric and fibrillar SNCA species appears to be critical to its the pathogenesis, yet it is still unclear what SNCA’s physiological function is. Recent discoveries implicating other such proteins, such as LRRK2 and MAPT, which do not to adhere to the SNCA centric model of PD, have muddied the waters. Equally, the finding through GWAS of multiple novel risk alleles with unknown or unclear modes of action complicate the picture still further. Such findings begin to make sense if, as there is significant evidence to suggest, sporadic PD is viewed as an accelerated variant of normal ageing, with multiple, possibly interacting, genetic predispositions, complemented potentially by epigenetic and environmental insults, resulting in dopaminergic cell death. The putative interaction between GBA and SNCA may serve as a template for such a multifaceted etiological model. Equally, a recurring finding across a spectrum of familial PD cell lines is that mitochondrial dysfunction, delivered by a variety of mechanisms, gives rise to the PD phenotype. These findings imply mitochondrial damage may be the common and irreversible downstream consequence of these mechanisms. Even more critical is why dopaminergic cells of the SNc are selectively vulnerable to PD-induced neuronal damage. Although significant progress has been made to date, this remains an unresolved question. Thus, although remarkable insights into the pathogenesis of PD have emerged in recent years, considerable work and many challenges remain before a coherent and comprehensive model can emerge. Principal among these will be reconciling the diverse and at times contradictory range of pathogenic mechanisms identified to date. It is clear that effective therapeutic interventions to slow the progress of PD will depend on an improved understanding of both its etiology and its pathogenesis.
ACKNOWLEDGMENTS

This work was funded by the Leonard Wolfson Experimental Neurology Center, the Wellcome Trust/MRC Joint Call in Neurodegeneration award (WT089698) to the UK Parkinson’s Disease Consortium (UKPDC), Parkinson’s UK, the Javon trust, the Kattan Trust and was supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

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