Chen *et al. Ageing Neur Dis* 2023;3:10
DOI: 10.20517/and.2023.05

Ageing and Neurodegenerative Diseases

Perspective

Open Access

Can alpha-synuclein be both the cause and a consequence of Parkinson's disease?

Kang Chen[1], Yu-Jie Guo[1], Peng Lei[1], David I Finkelstein[2]

[1]Department of Neurology and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China.
[2]Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria 3010, Australia.

Correspondence to: Prof. David I Finkelstein, Florey Institute of Neuroscience and Mental Health, 30 Royal Parade, University of Melbourne, Parkville, Victoria 3010, Australia. E-mail: david.finkelstein@florey.edu.au; Prof. Peng Lei, Department of Neurology and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No.17 People's South Road, Chengdu 610041, Sichuan, China. E-mail: peng.lei@scu.edu.cn

How to cite this article: Chen K, Guo YJ, Lei P, Finkelstein DI. Can alpha-synuclein be both the cause and a consequence of Parkinson's disease? *Ageing Neur Dis* 2023;3:10. https://dx.doi.org/10.20517/and.2023.05

Received: 28 Feb 2023 **First decision:** 13 Apr 2023 **Revised:** 18 Jun 2023 **Accepted:** 25 Jun 2023 **Published:** 28 Jun 2023

Academic Editor: Weidong Le **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

Alpha-synuclein (α-syn) is a presynaptic and nuclear protein that has been inextricably linked to Parkinson's disease (PD). It regulates the presynaptic activities of neurons, but its aggregation and spreading have been associated with a group of diseases termed synucleinopathies. Here, we examined the commonly held view that α-syn caused disease and explored the concept that α-syn aggregation may be a consequence of pathobiology. Future therapies may need to encompass α-syn both a cause and consequence of the disease process.

Keywords: Alpha-synuclein, Parkinson's disease, Lewy bodies, iron

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting approximately 7 million to 9 million people around the world[1], and the incidence of PD is growing even faster than that of Alzheimer's disease (AD)[1,2]. The Global Burden of Disease Study has estimated that there will be 12.9 million people suffering from PD by 2040[1], indicating increasing health expenses to individuals and societies.

PD is classically characterized by the degeneration of dopaminergic neurons in the substantia nigra *pars compacta* (SNpc). Within this region, there are Lewy bodies (LBs) and Lewy neurites (LNs) that are partially made from misfolded alpha-synuclein (α-syn), as well as elevated iron[3]. In addition to the SNpc, the pathogenesis of PD also affects a broad range of organs, including the gut, heart, eyes, and several other nuclei in the brain[4,5].

α-Syn is estimated to be 8.5% of the total protein content of the LBs[6]. Over the last few decades, α-syn is generally believed to contribute to the pathogenesis of PD, where excessive production of α-syn or its abnormal structure leads to aberrant aggregation that mediates disruption of cellular homeostasis[7]. Following the results from clinical and translational investigations studying α-syn, we here present an argument that α-syn can be both the cause and a consequence of PD. For example, genetic changes in the α-syn gene (*SNCA*) are sufficient to induce PD, which supports that α-syn is the cause of the disease. On the other hand, α-syn aggregation found in human PD may result from dysregulations of the brain biochemicals, and therefore it can be considered a consequence of the disease. This fact is essential since the evolution of new therapies may require an approach that encompasses both possibilities.

α-SYN BIOLOGY AND PATHOLOGY

α-Syn, which was first isolated from neural tissue in Pacific electric ray in 1988, is localized to the presynaptic nerve terminal[8]. In 1997, Polymeropoulos *et al.* discovered the first specific gene mutation associated with familial PD (A53T)[9-11]. The link between *SNCA* (which encodes α-syn protein) and PD has led to the development of antibodies against α-syn, which were applied to pathological sections of tissue from patients with PD[7].

α-Syn is a small protein composed of 143 amino acids and is about 15 kDa in size[12]. The N-terminal region (residues 1-60) of α-syn is mainly composed of seven highly conserved duplicated 11 residues (KTKEGV), with most of the known α-syn mutation sites[13,14]. The central nonamyloid component (NAC) region (residues 61-95) is composed of non-polar side chains, which are hydrophobic and tend to form β-sheet structures, resulting in its tendency to aggregate and toxicity[15,16]. The non-conserved C-terminal domain (residues 96-140) is negatively charged, and many phosphorylation sites are in this region, such as S129, Y125, Y133, and Y136[17], which are putatively thought to be critical for its aggregation and neurotoxicity [Figure 1]. In particular, phosphorylation of S129 was identified as the main posttranslational modification of α-syn in familial and sporadic Lewy body disease[18].

α-Syn is predominantly localized at presynaptic terminals, where it associates with synaptic vesicles[14]. The presynaptic location of synuclein and its interaction with membranes strongly indicate a role in endocytosis and exocytosis. In synuclein knockout mice, the action potentials were reduced, the synaptic structure was changed, and age-dependent neuronal dysfunction was observed[19]. A recent study found that the α-syn mutation (A53T and E46K) further accelerated the endocytosis of vesicles[20], collectively supporting a crucial role of α-syn in neuronal endocytosis.

Overexpression of α-syn in dopaminergic neurons of substantia nigra (SN) results in impaired neurotransmission, suggesting α-syn may play an attenuating role in neurotransmitter release[21,22]. Synapsins, members of the cytoplasmic regulatory family of synaptic vesicles (SV), promote the interaction between α-syn and synaptic vesicles[23]. α-syn can be inserted into the synapsin/SV liquid phase to facilitate SV clustering[23]. Additionally, the neurotransmitter release from presynaptic nerve terminals requires a cycle of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE)-complex assembly and disassembly, where α-syn is directly bound to the SNARE-complex (v-SNARE and t-SNARE) and

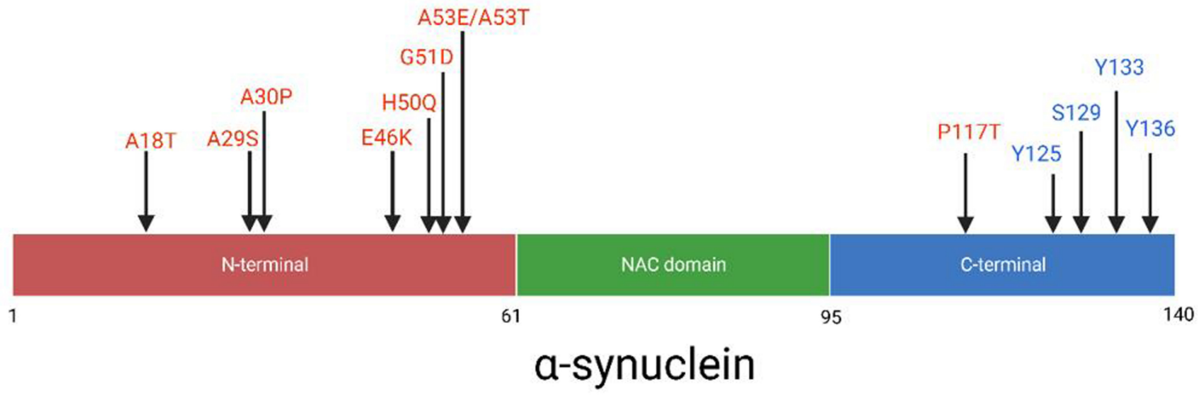

Figure 1. Schematic structure of α-synuclein. The arrows indicate disease-related mutations (red) and phosphorylation sites (blue). NAC: Nonamyloid component.

promotes its assembly[24,25]. α-Syn oligomers may sequester the v-SNARE using multiple binding sites for t-SNARE on vesicles and inhibit SNARE-mediated vesicle fusion[26]. Moreover, α/β/γ-synuclein triple knockout mice exhibited an age-dependent decrease in SNARE-complex assembly, leading to neurological impairments[25].

EVIDENCE SUPPORTING α-SYN AS THE CAUSE OF PD

The genetic evidence from the *SNCA* gene

Both rare point mutations and copy number gains of *SNCA* genes have been reported to lead to autosomal dominant PD. The frequency of *SNCA* mutations in sporadic and familial PD is approximately 0.2% and 1%-2%, respectively[27]. These point mutations of *SNCA* include A53T, A30P, E46K, A53E, H50Q, G51D, A18T, and A29S[13,28], and *SNCA* may be duplicated or triplicated [Table 1].

These carriers of the A53T (age of onset 35-59 years old) mutation have an approximately 10-year earlier onset than the other mutations [e.g., A30P (54-76 years old), E46K (50-69 years old), and H50Q (54-70 years old)[29]]. Both A53T and A30P mutations accelerate the aggregation of α-syn[30]. Mouse models that overexpress the human α-syn A53T exhibit progressive neurodegeneration in the SN, and age-dependent motor and non-motor symptoms of PD[31]. The H50Q mutation has been reported to strongly stabilize α-syn fibrils and significantly accelerate their aggregation and amyloid formation[32]. The age of onset, clinical features, and progression of the patients with G51D mutation are most similar to the *SNCA* triplication and A53T mutations[33]. They are frequently associated with early-onset PD as well as cognitive impairment and hallucinations[33]. A53E (40-60 years old) mutation was found to attenuate α-syn aggregation and amyloid formation[34]; however, it increases the cellular toxicity induced by MPP+[32]. The A18T (50 years old) and A29S (60 years old) mutations were first found in sporadic PD[35], and they promote α-syn fibrillation and cytotoxicity[35,36]. There was also a P117T variant reported in thirteen subjects without symptoms of PD[28].

Multiplications of the *SNCA* gene have been reported to cause PD as well. *SNCA* duplication results in clinical phenotypes similar to idiopathic PD[37], including a relatively late onset of age and slowly progressed neurodegeneration, which was first identified in a French family[38]. Interestingly, *SNCA* duplication may not consistently cause parkinsonism, as cognitive impairment has been observed in carriers without parkinsonism[39]. This seems to be a common phenomenon in neurodegenerative diseases, as the duplication of *MAPT*, the gene encoding tau protein, also causes neurodegeneration[40-42]. In contrast, *SNCA* triplication resulted in a much earlier onset of the disease and rapid progression, as has been reported in

Table 1. Major genetic causes associated with Parkinsonism and synuclein pathology

Gene	Mutation	Prevalence in PD population	Alpha syn pathology	References
SNCA	A53T	1.39%-4.5%	Cortical and subcortical LB distribution is different from iPD. Some with LBs in the hypothalamus and amygdala. Neuronal loss and gliosis exist in the amygdala.	[43,140-146]
	A30P	2.51%		
	E46K	2.97%		
	H50Q	0.22%		
	G51D	0.9%		
	Duplication	0.045%		
	Triplication	1.14%-2.86%		
LRRK2	G2019S	0.54%-5.1%	SN and LC neurons degeneration and LBs formation. 64.7% of people with LB. LB pathology in SN and LC. Some with LB in the amygdala, prefrontal, and motor cortices.	[117-119,142,147-149]
PINK1	-	1.14%-6.9%	Loss of neurons in SNpc. Two case studies show the absence of Lewy pathology, while another study showed a family with LB and aberrant neurites in the reticular nuclei, SNpc, and Meynert nucleus, but none in LC.	[150-156]
PRKN	-	4.55%-17%	Neuronal degeneration, LB pathology in 16.7%-37.5% people. No Lewy pathology in the hippocampus or cerebral cortex. Some without LB in the SNpc. SNpc neuronal loss is as severe as in iPD.	[119,129,154,157,158]
GBA	-	7%-15%	Widespread and abundant α-syn pathology in all *GBA* mutation carriers, increased frequency of diffuse neocortical Lewy body-type pathology.	[159-163]

The majority of cases of Parkinson's are idiopathic, with up to 20% associated with a genetic cause and termed parkinsonism. Parkinsonism varies from iPD in the age of onset and symptoms. This table focuses on the synuclein pathology of those cases with a genetic association. *GBA*: Glucocerebrosidase; iPD: idiopathic Parkinson's disease; LB: lewy body; LC: locus coeruleus; *LRRK2*: leucine-rich repeat kinase 2; *PINK1*: PTEN-induced putative kinase 1; *PRKN*: parkin gene; SN: substantia nigra; *SNCA*: α-syn gene.

several races[43-45]. Collectively, it suggests that the copy number of *SNCA* may increase the disease severity, supporting the notion that α-syn may be the cause of PD.

α-Syn injection models of PD

Besides genetic evidence, recently utilized α-syn injection models also support the notion that a single protein may cause the disease. In 2012, Luk *et al.* reported that intra-striatal inoculation of mouse α-syn preformed fibrils (PFF) in WT mice induced LBs/LNs pathology, dopaminergic neuron loss, and motor deficits[46]. Such results have been robustly repeated, and several studies have injected α-syn PFFs into different brain regions to investigate its spreading in the brain[47-49].

Olfactory bulbs (OB) are thought to be the first places where α-syn pathology appears[50,51]. Injection of α-syn PFFs into the OB of WT mice resulted in the spreading of α-syn pathology trans-neuronally to over 40 other brain regions, including the amygdala, entorhinal cortex, locus coeruleus (LC), and SNpc[52]. However, these mice presented no alteration of locomotion or anxiety level with deficits in odor discrimination[53].

The SN is the most severely damaged brain region in PD, and indeed injection of α-syn PFFs directly into the SN promoted α-syn accumulation in the SNpc and striatum, activated microglia in the SN, reduced dopaminergic neuron number, and caused striatal degeneration[54]. The brain homogenates of mice with LB pathology were also injected into the cortex and striatum of WT mice, and α-syn deposition was found across the brain[55].

Systemic administration of α-syn also triggers selective neuronal pathology as seen in PD[56]. Inoculation of α-syn preformed fibrils in the duodenum results in intestinal nervous system dysfunction, increased midbrain dopaminergic neuronal death, and brain stem α-syn pathology, with motor impairment[57]. When injected into the tail vein, the mice exhibited gastrointestinal and olfactory dysfunction, with neuronal

degeneration in the midbrain and brain stem[56], mimicking the sequence of pathological events that occurred in PD. In addition, oral or intraperitoneal administration of α-syn can induce α-syn pathology in the brain[58], where intranasally inoculation additionally triggers iron accumulation in microglia but not dopaminergic neuronal loss nor behavioral dysfunction[59].

EVIDENCE SUPPORTING α-SYN AS A CONSEQUENCE OF PATHOBIOLOGY IN PD

How α-syn aggregates and spreads in PD

How does Lewy pathology spread in the brain of humans with PD? Braak *et al.* proposed that misfolded α-syn spreads from a few cells to multiple brain regions over years or decades[60]. They divided PD pathology into six stages[60]. At stages 1 and 2, Lewy pathology is only within the medulla oblongata. In the early symptomatic stage (3 and 4), α-syn inclusions occur in SN, the anteromedial temporal mesocortex, and the brain stem. At stages 5 and 6, Lewy pathology in the area previously described becomes more severe; the pathology continues to spread to the adjoining high-order sensory association areas of the neocortex. However, it is important to note that only about half of the human studies show a distribution of Lewy pathology in the brain consistent with the Braak staging model[61]. A more recent imaging study raised the hypotheses of an alternative model of transmission of α-syn in PD[62], including brain-first and body-first symptoms. The pathology of the body-first (from bottom to top) subtype originated from the intestinal or surrounding autonomous nervous system, then rose to the brain through the vagus nerve. The pathology of the brain-first (from top to bottom) subtype is initially present in the brain itself, presenting as REM sleep behavior disorder (RBD) and then descending to other tissues (heart, gut).

Either working model of α-syn spreading in human PD initiated from α-syn aggregates is more likely triggered by other factors, unlike the materials injected into the mice brains. *In vitro* studies have confirmed that these aggregates, either oligomers or fibrils, are neurotoxic[63,64]. Therefore, it is necessary to study the inducement of α-syn oligomer formation and fibrosis. These factors include dopamine[65], lipids[66], metal[67], and others.

Dopamine (DA) and its analogs or metabolites can regulate α-syn aggregation[68,69], and in PD, dopamine reduction in the SNpc as a consequence of SN neuronal loss directly causes motor disability[70]. Hence, the supplementation of DA medications temporally restores motor functions and increases the lifespan of PD patients[71,72]. It has been found that, at least in models of PD, the enrichment of dopamine with iron distinguished SN from nearby regions, such as the ventral tegmental area (VTA), as the valuable brain region for parkinsonism[73]. Such enrichment also provides a highly active chemical environment for α-syn aggregation. Importantly it has been reported that α-syn forms SDS-resistant soluble oligomers in the presence of dopamine[74], which in turn depolymerizes fibrils[75]. The mechanism was investigated, and it is suggested that the oxidation of dopamine resulted in the accumulation of dopamine quinone in the cytoplasm, which interacts with α-syn to inhibit the conversion of oligomers into fibrils[75]. In addition, α-syn also plays a role in regulating dopamine biosynthesis[76]. A loss of soluble α-syn, by reduced expression or promoted aggregation, increases dopamine synthesis with an accompanying increase in reactive dopamine metabolites[76].

An elevation of iron in the SNpc was first observed in the brains of PD patients in 1924[77], which subsequently was confirmed by several studies[3,78-82]. Interestingly, the increase of iron differs across cell types in PD. Dopaminergic neurons in the SN of PD patients exhibit a twofold increase in cellular iron levels[83,84], whereas the iron content of astrocytes remains unchanged. Microglia show an accumulation of about 25%, while Olig2-stained oligodendroglia exhibit an increase of nearly 150%[84]. Since nigral iron accumulation in PD is correlated with disease motor severity and dopaminergic neurodegeneration[85,86], it is

hypothesized that iron participates in PD pathogenesis[87] and the mechanism of its accumulation has been linked with tau-APP (Amyloid Precursor Protein) dysfunction in PD[82,88-91]. Biochemically, iron directly binds to α-syn and promotes α-syn aggregation in a dose-dependent manner[67,87,92-94]. An iron reactive element (IRE) has been found in the RNA of α-syn[95-97]. Iron regulatory proteins (IRP) can bind to the IRE of α-syn mRNA and inhibits the translation of α-syn transcripts. However, iron can bind to IRP, leading to the separation of IRP and IRE, thereby promoting α-syn expression and aggregation[98,99]. Indirectly, iron also promotes aggregation or oligomer formation of α-syn by regulating the phosphorylation of α-syn[100]. In both human and animal models of PD, preclinical studies using iron-modulating agents have been tested to reduce α-syn aggregation and toxicity[93,101-103]. PBT434, a novel quinazolinone compound, binds to iron, significantly reduces iron-mediated α-syn aggregation, rescues the loss of SN dopaminergic neurons, and ameliorates motor dysfunction in PD mouse models[93]. Interestingly, a recent study found that brain iron enrichment attenuated α-syn diffusion in a dose-dependent manner after α-syn PFF injection in mice[104]. In addition to iron, copper and zinc also interact with α-syn[105,106]. In PD cases, copper is dysregulated[105]. Copper binding to α-syn with a higher affinity at the residues 48-53 induces aggregation of α-syn[107]. Copper binding leads to the exposure of highly amyloidogenic NAC region of α-syn, which increases fibril formation[107]. Zinc ions have been reported to directly interact with α-syn and promote its aggregation[106], where it displayed the modulation effects on the secondary structures of the α-syn NAC region[108].

In PD, LBs have been reported to contain membrane fragments, vesicles, and organelles including mitochondria and lysosomes, suggesting that disruption of neuronal membrane homeostasis may occur in PD and may participate in α-syn aggregation[66]. α-syn aggregation may be triggered by the destruction of its affinity for the membrane. The lipid/α-syn ratio was suggested as one important factor for determining α-syn aggregation under quiescent conditions[109]. Under physiological conditions, the lipid/α-syn ratio is high, and limited monomeric α-syn is present freely in cells since excess lipid maintains α-syn to bind to the membrane surface in a helical conformation. The reduction of the lipid/α-syn ratio during PD reduced the binding between α-syn and the cell membrane and α-syn was released available for aggregation. Only a fraction of vesicle-bound α-syn was able to serve as an active nucleation seed to initiate aggregation[110]; however, the release of α-syn to cytosol greatly promotes the nucleation process on the lipid surface, hence promoting the aggregation. On the other hand, the promoted aggregation leads to lowered lipid/α-syn ratios[110], making it a vicious cycle.

Furthermore, growing epidemiological evidence links PD risk to immune disorders and certain infections[111]. Recent research has suggested that the upregulation of α-syn levels is a typical response to infections[112,113]. Especially under specific circumstances, such as genetic predisposition and dysregulated inflammatory response due to aging, monomer α-syn may aggregate into oligomers[114]. These oligomers are then transported by nerve endings and can accumulate in the central nervous system, form pathogenic fibrils, and trigger neurodegeneration[114,115].

Other genes are associated with α-syn pathology

Additionally, it is unlikely that the aggregation process of α-syn initiated spontaneously, and several genes have been identified to cause PD, including leucine-rich repeat kinase 2 (*LRRK2*), Parkin gene (*PRKN*), PTEN-induced putative kinase 1 (*PINK1*), and Glucocerebrosidase (*GBA*) [Table 1]. Most of which present with α-syn pathology, especially *LRRK2* and *PRKN*. In these cases, the genetic mutations of individual genes other than *SNCA* are primarily responsible for parkinsonism and synuclein deposition, as seen in idiopathic PD.

LRRK2 is a serine/threonine kinase[116], and clinical results showed that SN and LC neurons were lost in PD patients with G2019S mutation, and 64.7% of patients were accompanied by LB pathology in SN and LC[117-119] and similar motor phenotype and progression as in idiopathic Parkinson's disease (iPD)[120]. In mice, the mutation caused enhanced α-syn aggregation and propagation, with significant loss of SN dopaminergic neurons accompanied by motor dysfunction[121]. In rodents, inhibitors of *LRRK2* kinase activity reduce α-syn pathology, which may be related to activating the autophagic lysosomal pathway[122,123]. A recent study found that *LRRK2* also promotes a neuroinflammatory cascade by phosphorylation and inducing nuclear translocation of NFATc2, blocking α-syn clearance in microglia of mice; in addition, NFATc2 expression levels and immune reactivity were increased in PD patients[124].

Parkin, encoded by the *PRKN* gene, was identified in 1998 from a patient who exhibited an early onset of parkinsonism but with slower progression[125] and less cognitive impairment than in iPD[126]. It is the most common factor (10%-20%) for early onset PD across ethnic groups, which typically develops in carriers before age 41 to 50[119]. It is an E3 ubiquitin ligase protein composed of a Ubl domain, a large unstructured loop, and four zinc-binding domains[127]. The main pathological feature of Parkin PD is the loss of SN neurons, but only 16.7%-37.5% of patients with LB pathology in SN and LC[128,129]. Overexpression of parkin was reported to prevent neurodegeneration induced by α-syn in rats expressing human A30P α-synuclein[130], and elevated oxidative stress seen in PD affects parkin ligase activity by altering its posttranslational modification[131]. It is hypothesized that parkin may be essential for LB formation even though the mutation carriers don't typically exhibit LB pathology.

DISCUSSIONS

It is a commonly held view that α-syn has a central role in the pathogenesis of PD and other α-synucleinopathies. We reviewed the evidence and concluded that α-syn can be both a cause and a pathological consequence of the disease in different conditions. On the one hand, genetic changes in the *SNCA* are sufficient to induce PD, as well as α-syn aggregation injections into the animals, which support that α-syn can cause the disease, or at least the symptoms of PD. On the other hand, α-syn aggregation found in human PD may result from dysregulation of the brain chemicals such as dopamine or iron, and therefore it can be considered a consequence of the disease [Figure 2]. In addition, mutations of several other genes also result in parkinsonism and α-syn deposition, further supporting the notion that α-syn is not the only cause of the disease.

Incidental Lewy body disease (iLBD) describes people with LBs or LNs but without clinical symptoms of parkinsonism or dementia. Clinical studies showed that the distribution of LBs in iLBD was similar to that in PD[132]. Compared with the normal control group, the neuron density of locus coeruleus (LC) was significantly reduced, and the TH immunoreactivity in the striatum and the epicardial sympathetic fiber was decreased[133], but this reduction was not as severe as that in the PD group. These suggested that incidental Lewy body disease may be pre-symptomatic PD. Importantly, both studies in humans and monkeys have shown an age-related accumulation of α-syn aggregation and LBs decades before any disease[134]. These suggest that there may be some threshold effect when normal age-related nigral cell loss is accelerated or a "tipping point" of α-syn increase and clinical disease. However, when the disease reaches a critical point, iLBD exhibits symptoms of PD. Here nor can LB be treated only as a symptom, shown as an example of the complex role of α-syn in disease.

The multiple roles of α-syn in PD are similar to other misfolded proteins in neurodegenerative diseases. For example, genetic mutations in the amyloid precursor protein (APP) cause Alzheimer's disease (AD)[135], and direct injection of Aβ oligomers into the hippocampus of wild-type mice also causes cognitive impairment

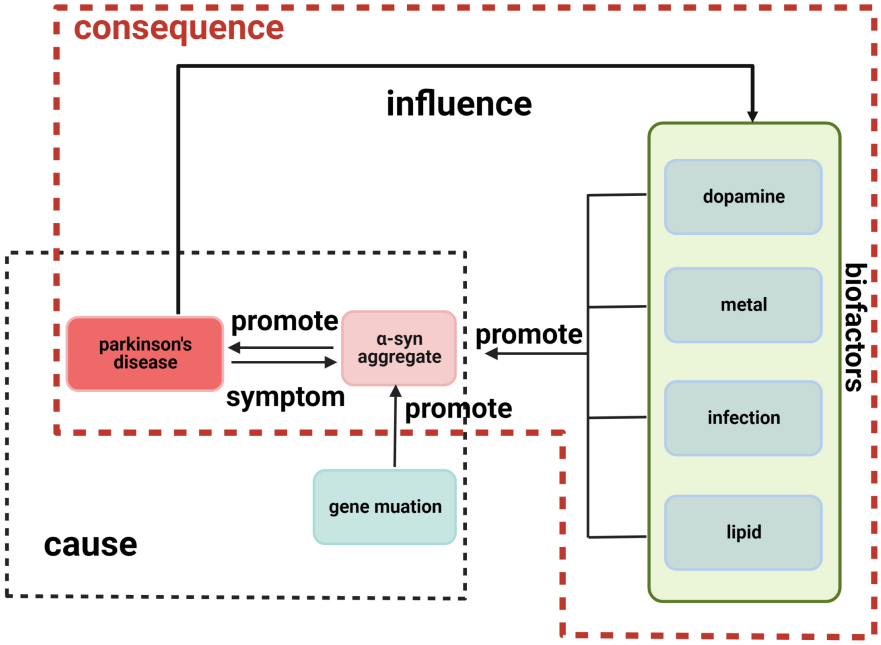

Figure 2. α-Synuclein can be both the cause and a consequence of Parkinson's disease.

and hippocampal neuron loss[136]. On the other hand, A typical symptom of AD is the deposition of amyloid beta (Aβ)[137], modified by several factors. In this case, Aβ is also both cause and consequence of AD. Currently, therapies targeting antibodies against Aβ have been approved for clinical use[138], with limited understanding of their mechanisms and characteristics. And these anti-Aβ antibodies can cause other side effects[138,139]. For example, anti-Aβ therapy can damage long-term brain health by accelerating brain atrophy[139]. Therefore, we still have doubts about Aβ therapies. Removing plaque may not result in the expected improvements, since the factors promoting plaque formation were not limited. This is an essential question as the evolution of new therapies may require an approach that encompasses both possibilities.

Currently, α-syn targeted therapy in synucleinopathies is mainly aimed at eliminating α-syn aggregation. Understanding that α-syn can be both the cause and a consequence of disease under different circumstances is critical for future mechanistic studies and drug discoveries.

DECLARATIONS

Authors' contributions

Conceived the review: Finkelstein DI, Lei P
Wrote and edited the manuscript: Chen K, Lei P, Finkelstein DI
Critically revised the work: Guo YJ

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by grants from the National Natural Science Foundation of China (82071191, 32000724) and the West China Hospital 1.3.5 project for disciplines of excellence (ZYYC20009).

Conflict of interest

Both Finkelstein DI and Lei P served as editorial members of Ageing and Neurodegenerative Diseases, and Lei P is the Guest Editor of this Special Issue "Ferroptosis in Neurological Disorders". Neither Finkelstein DI nor Lei P was involved in the editorial process of the work.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Dorsey ER, Bloem BR. The Parkinson pandemic - a call to action. *JAMA Neurol* 2018;75:9-10. DOI PubMed
2. GBD 2015 Neurological Disorders Collaborator Group. Global, regional, and national burden of neurological disorders during 1990-2015: a systematic analysis for the global burden of disease study 2015. *Lancet Neurol* 2017;16:877-97. DOI PubMed PMC
3. Dexter DT, Wells FR, Lee AJ, et al. Increased nigral iron content and alterations in other metal ions occurring in brain in Parkinson's disease. *J Neurochem* 1989;52:1830-6. DOI PubMed
4. Gonçalves VC, Cuenca-bermejo L, Fernandez-Villalba E, et al. Heart matters: cardiac dysfunction and other autonomic changes in Parkinson's disease. *Neuroscientist* 2022;28:530-42. DOI PubMed
5. Matzaras R, Shi K, Artemiadis A, et al. Brain neuroimaging of rapid eye movement sleep behavior disorder in Parkinson's disease: a systematic review. *J Parkinsons Dis* 2022;12:69-83. DOI PubMed
6. Mccormack A, Chegeni N, Chegini F, et al. Purification of α-synuclein containing inclusions from human post mortem brain tissue. *J Neurosci Methods* 2016;266:141-50. DOI PubMed
7. Stefanis L. α-Synuclein in Parkinson's disease. *Cold Spring Harb Perspect Med* 2012;2:a009399. DOI PubMed PMC
8. Maroteaux L, Campanelli J, Scheller RH. Synuclein: a neuron-specific protein localized to the nucleus and presynaptic nerve terminal. *J Neurosci* 1988;8:2804-15. DOI PubMed PMC
9. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha - synuclein gene identified in families with Parkinson's disease. *Science* 1997;276:2045-7. DOI PubMed
10. Peña-Díaz S, García-Pardo J, Ventura S. Development of small molecules targeting α-synuclein aggregation: a promising strategy to treat Parkinson's disease. *Pharmaceutics* 2023;15:839. DOI PubMed PMC
11. Yi S, Wang L, Wang H, Ho MS, Zhang S. Pathogenesis of α-synuclein in Parkinson's disease: from a neuron-glia crosstalk perspective. *Int J Mol Sci* 2022;23:14753. DOI PubMed PMC
12. Calabresi P, Mechelli A, Natale G, Volpicelli-Daley L, Di Lazzaro G, Ghiglieri V. Alpha-synuclein in Parkinson's disease and other synucleinopathies: from overt neurodegeneration back to early synaptic dysfunction. *Cell Death Dis* 2023;14:176. DOI PubMed PMC
13. Guo YJ, Xiong H, Chen K, Zou JJ, Lei P. Brain regions susceptible to alpha -synuclein spreading. *Mol Psychiatry* 2022;27:758-70. DOI PubMed
14. Wong YC, Krainc D. α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. *Nat Med* 2017;23:1-13. DOI PubMed PMC
15. El-Agnaf OM, Jakes R, Curran MD, et al. Aggregates from mutant and wild-type alpha-synuclein proteins and NAC peptide induce apoptotic cell death in human neuroblastoma cells by formation of beta-sheet and amyloid-like filaments. *FEBS Lett* 1998;440:71-5. DOI PubMed
16. Pfefferkorn CM, Jiang Z, Lee JC. Biophysics of α-synuclein membrane interactions. *Biochim Biophys Acta* 2012;1818:162-71. DOI PubMed PMC
17. Oueslati A, Fournier M, Lashuel HA. Role of post-translational modifications in modulating the structure, function and toxicity of α-synuclein: implications for Parkinson's disease pathogenesis and therapies. *Prog Brain Res* 2010;183:115-45. DOI PubMed
18. Anderson JP, Walker DE, Goldstein JM, et al. Phosphorylation of Ser-129 is the dominant pathological modification of alpha-synuclein in familial and sporadic Lewy body disease. *J Biol Chem* 2006;281:29739-52. DOI PubMed

19. Greten-Harrison B, Polydoro M, Morimoto-Tomita M, et al. αβγ-Synuclein triple knockout mice reveal age-dependent neuronal dysfunction. *Proc Natl Acad Sci U S A* 2010;107:19573-8. DOI PubMed PMC
20. Schechter M, Atias M, Abd Elhadi S, Davidi D, Gitler D, Sharon R. α-Synuclein facilitates endocytosis by elevating the steady-state levels of phosphatidylinositol 4,5-bisphosphate. *J Biol Chem* 2020;295:18076-90. DOI PubMed PMC
21. Lundblad M, Decressac M, Mattsson B, Björklund A. Impaired neurotransmission caused by overexpression of α-synuclein in nigral dopamine neurons. *Proc Natl Acad Sci U S A* 2012;109:3213-9. DOI PubMed PMC
22. Wang L, Das U, Scott D, Tang Y, Mclean P, Roy S. α-Synuclein multimers cluster synaptic vesicles and attenuate recycling. *Curr Biol* 2014;24:2319-26. DOI PubMed PMC
23. Atias M, Tevet Y, Sun J, et al. Synapsins regulate α-synuclein functions. *Proc Natl Acad Sci U S A* 2019;116:11116-8. DOI PubMed PMC
24. Yoo G, Shin Y, Lee NK. The Role of α-synuclein in SNARE-mediated synaptic vesicle fusion. *J Mol Biol* 2023;435:167775. DOI PubMed
25. Burré J, Sharma M, Tsetsenis T, Buchman V, Etherton MR, Südhof TC. Alpha-synuclein promotes SNARE-complex assembly in vivo and in vitro. *Science* 2010;329:1663-7. DOI PubMed PMC
26. Choi B, Choi M, Kim J, et al. Large α-synuclein oligomers inhibit neuronal SNARE-mediated vesicle docking. *Proc Natl Acad Sci U S A* 2013;110:4087-92. DOI PubMed PMC
27. Lunati A, Lesage S, Brice A. The genetic landscape of Parkinson's disease. *Rev Neurol* 2018;174:628-43. DOI PubMed
28. Blauwendraat C, Makarious MB, Leonard HL, et al. A population scale analysis of rare SNCA variation in the UK biobank. *Neurobiol Dis* 2021;148:105182. DOI PubMed PMC
29. Kasten M, Klein C. The many faces of alpha-synuclein mutations. *Mov Disord* 2013;28:697-701. DOI PubMed
30. Narhi L, Wood SJ, Steavenson S, et al. Both familial Parkinson's disease mutations accelerate α-synuclein aggregation. *J Biol Chem* 1999;274:9843-6. DOI PubMed
31. Jiao L, Du X, Jia F, et al. Early low-dose ghrelin intervention via miniosmotic pumps could protect against the progressive dopaminergic neuron loss in Parkinson's disease mice. *Neurobiol Aging* 2021;101:70-8. DOI PubMed
32. Petrucci S, Ginevrino M, Valente EM. Phenotypic spectrum of alpha-synuclein mutations: new insights from patients and cellular models. *Parkinsonism Relat Disord* 2016;22:S16-20. DOI PubMed
33. Kiely AP, Asi YT, Kara E, et al. α-Synucleinopathy associated with G51D SNCA mutation: a link between Parkinson's disease and multiple system atrophy? *Acta Neuropathol* 2013;125:753-69. DOI PubMed PMC
34. Ghosh D, Sahay S, Ranjan P, et al. The newly discovered Parkinson's disease associated finnish mutation (A53E) attenuates α-synuclein aggregation and membrane binding. *Biochemistry* 2014;53:6419-21. DOI PubMed
35. Hoffman-zacharska D, Koziorowski D, Ross OA, et al. Novel A18T and pA29S substitutions in α-synuclein may be associated with sporadic Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:1057-60. DOI PubMed PMC
36. Kumar S, Jangir DK, Kumar R, Kumari M, Bhavesh NS, Maiti TK. Role of sporadic parkinson disease associated mutations A18T and A29S in enhanced α-synuclein fibrillation and cytotoxicity. *ACS Chem Neurosci* 2018;9:230-40. DOI PubMed
37. Ibáñez P, Bonnet A, Débarges B, et al. Causal relation between α-synuclein locus duplication as a cause of familial Parkinson's disease. *The Lancet* 2004;364:1169-71. DOI
38. Chartier-harlin M, Kachergus J, Roumier C, et al. Alpha-synuclein locus duplication as a cause of familial Parkinson's disease. *Lancet* 2004;364:1167-9. DOI PubMed
39. Kéri S, Moustafa AA, Myers CE, Benedek G, Gluck MA. {alpha}-Synuclein gene duplication impairs reward learning. *Proc Natl Acad Sci U S A* 2010;107:15992-4. DOI PubMed PMC
40. Rovelet-Lecrux A, Hannequin D, Guillin O, et al. Frontotemporal dementia phenotype associated with MAPT gene duplication. *J Alzheimers Dis* 2010;21:897-902. DOI PubMed
41. Guennec K, Quenez O, Nicolas G, et al; The CNR-MAJ collaborators. 17q21.31 duplication causes prominent tau-related dementia with increased MAPT expression. *Mol Psychiatry* 2017;22:1119-25. DOI PubMed
42. Chen Z, Chen JA, Shatunov A, et al; NNIPPS and BBBIPPS Study Groups. Genome□wide survey of copy number variants finds MAPT duplications in progressive supranuclear palsy. *Mov Disord* 2019;34:1049-59. DOI PubMed
43. Singleton AB, Farrer M, Johnson J, et al. α-Synuclein locus triplication causes Parkinson's disease. *Science* 2003;302:841. DOI PubMed
44. Farrer M, Kachergus J, Forno L, et al. Comparison of kindreds with parkinsonism and alpha-synuclein genomic multiplications. *Ann Neurol* 2004;55:174-9. DOI PubMed
45. Sekine T, Kagaya H, Funayama M, et al. Clinical course of the first Asian family with Parkinsonism related to SNCA triplication. *Mov Disord* 2010;25:2871-5. DOI PubMed
46. Luk KC, Kehm V, Carroll J, et al. Pathological α-synuclein transmission initiates parkinson-like neurodegeneration in nontransgenic mice. *Science* 2012;338:949-53. DOI PubMed PMC
47. Chu Y, Muller S, Tavares A, et al. Intrastriatal alpha-synuclein fibrils in monkeys: spreading, imaging and neuropathological changes. *Brain* 2019;142:3565-79. DOI PubMed PMC
48. Bassil F, Meymand ES, Brown HJ, et al. α-Synuclein modulates tau spreading in mouse brains. *J Exp Med* 2021;218:e20192193. DOI PubMed PMC
49. Wu Q, Shaikh MA, Meymand ES, et al. Neuronal activity modulates alpha-synuclein aggregation and spreading in organotypic brain

slice cultures and in vivo. *Acta Neuropathol* 2020;140:831-49. DOI PubMed PMC
50. Mason DM, Nouraei N, Pant DB, et al. Transmission of α-synucleinopathy from olfactory structures deep into the temporal lobe. *Mol Neurodegener* 2016;11:49. DOI PubMed PMC
51. Rey NL, Petit GH, Bousset L, Melki R, Brundin P. Transfer of human α-synuclein from the olfactory bulb to interconnected brain regions in mice. *Acta Neuropathol* 2013;126:555-73. DOI PubMed PMC
52. Rey NL, George S, Steiner JA, et al. Spread of aggregates after olfactory bulb injection of α-synuclein fibrils is associated with early neuronal loss and is reduced long term. *Acta Neuropathol* 2018;135:65-83. DOI PubMed PMC
53. Rey NL, Steiner JA, Maroof N, et al. Widespread transneuronal propagation of α-synucleinopathy triggered in olfactory bulb mimics prodromal Parkinson's disease. *J Exp Med* 2016;213:1759-78. DOI PubMed PMC
54. Harms AS, Delic V, Thome AD, et al. α-Synuclein fibrils recruit peripheral immune cells in the rat brain prior to neurodegeneration. *Acta Neuropathol Commun* 2017;5:85. DOI PubMed PMC
55. Luk KC, Kehm VM, Zhang B, O'brien P, Trojanowski JQ, Lee VM. Intracerebral inoculation of pathological α-synuclein initiates a rapidly progressive neurodegenerative α-synucleinopathy in mice. *J Exp Med* 2012;209:975-86. DOI PubMed PMC
56. Kuan W, Stott K, He X, et al. Systemic α-synuclein injection triggers selective neuronal pathology as seen in patients with Parkinson's disease. *Mol Psychiatry* 2021;26:556-67. DOI PubMed PMC
57. Challis C, Hori A, Sampson TR, et al. Gut-seeded α-synuclein fibrils promote gut dysfunction and brain pathology specifically in aged mice. *Nat Neurosci* 2020;23:327-36. DOI PubMed PMC
58. Lohmann S, Bernis ME, Tachu BJ, Ziemski A, Grigoletto J, Tamgüney G. Oral and intravenous transmission of α-synuclein fibrils to mice. *Acta Neuropathol* 2019;138:515-33. DOI PubMed PMC
59. Guo J, Yue F, Song D, et al. Intranasal administration of α-synuclein preformed fibrils triggers microglial iron deposition in the substantia nigra of macaca fascicularis. *Cell Death Dis* 2021;12:81. DOI PubMed PMC
60. Braak H, Tredici KD, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 2003;24:197-211. DOI PubMed
61. Surmeier DJ, Obeso JA, Halliday GM. Selective neuronal vulnerability in Parkinson disease. *Nat Rev Neurosci* 2017;18:101-13. DOI PubMed PMC
62. Horsager J, Andersen KB, Knudsen K, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain* 2020;143:3077-88. DOI PubMed
63. Yang W, Li X, Yin N. α-Syn oligomers incubated with Parkinson's disease plasma promote neuron damage. *Int J Clin Exp Pathol* 2020;13:1995-2008. Available from: https://pubmed.ncbi.nlm.nih.gov/32922594/.
64. Volpicelli-daley L, Luk K, Patel T, et al. Exogenous α-synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* 2011;72:57-71. DOI PubMed PMC
65. Cappai R, Leck S, Tew DJ, et al. Dopamine promotes alpha□synuclein aggregation into SDS□resistant soluble oligomers via a distinct folding pathway. *FASEB J* 2005;19:1377-9. DOI PubMed
66. Mori A, Imai Y, Hattori N. Lipids: key players that modulate α-synuclein toxicity and neurodegeneration in Parkinson's disease. *Int J Mol Sci* 2020;21:3301. DOI PubMed PMC
67. Song N, Xie J. Iron, dopamine, and α-synuclein interactions in at-risk dopaminergic neurons in Parkinson's disease. *Neurosci Bull* 2018;34:382-4. DOI PubMed PMC
68. Galvin JE. Interaction of alpha-synuclein and dopamine metabolites in the pathogenesis of Parkinson's disease: a case for the selective vulnerability of the substantia nigra. *Acta Neuropathol* 2006;112:115-26. DOI PubMed
69. Latawiec D, Herrera F, Bek A, et al. Modulation of alpha-synuclein aggregation by dopamine analogs. *PLoS One* 2010;5:e9234. DOI PubMed PMC
70. Aarsland D, Batzu L, Halliday GM, et al. Parkinson disease-associated cognitive impairment. *Nat Rev Dis Primers* 2021;7:47. DOI PubMed
71. Rajput AH. Levodopa prolongs life expectancy and is non-toxic to substantia nigra. *Parkinsonism Relat Disord* 2001;8:95-100. DOI PubMed
72. Med Collaborative Group. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet* 2014;384:1196-205. DOI PubMed
73. Hare DJ, Lei P, Ayton S, et al. An iron-dopamine index predicts risk of parkinsonian neurodegeneration in the substantia nigra pars compacta. *Chem Sci* 2014;5:2160-9. DOI
74. Lee H, Baek SM, Ho D, Suk J, Cho E, Lee S. Dopamine promotes formation and secretion of non-fibrillar alpha-synuclein oligomers. *Exp Mol Med* 2011;43:216-22. DOI PubMed PMC
75. Leong SL, Cappai R, Barnham KJ, Pham CLL. Modulation of α-synuclein aggregation by dopamine: a review. *Neurochem Res* 2009;34:1838-46. DOI PubMed
76. Perez RG, Waymire JC, Lin E, Liu JJ, Guo F, Zigmond MJ. A role for α-synuclein in the regulation of dopamine biosynthesis. *J Neurosci* 2002;22:3090-9. DOI PubMed PMC
77. Lhermitte J, Kraus WM, Mcalpine D. Original papers: on the occurrence of abnormal deposits of iron in the brain in parkinsonism with special reference to its localisation. *J Neurol Psychopathol* 1924;5:195-208. DOI PubMed PMC
78. Hirsch EC, Brandel J, Galle P, Javoy-agid F, Agid Y. Iron and aluminum increase in the substantia nigra of patients with Parkinson's

disease: an X-ray microanalysis. *J Neurochem* 1991;56:446-51. DOI PubMed

79. Xiong H, Tuo Q, Guo Y, Lei P. Diagnostics and treatments of iron-related CNS diseases. In: Chang Y, editor. Brain Iron Metabolism and CNS Diseases. Singapore: Springer; 2019. pp. 179-94. DOI
80. Lei P, Ayton S, Bush AI. Axonal dispatch of iron in neuronal signaling. *Nat Chem Biol* 2019;15:1135-6. DOI PubMed
81. Dexter DT, Carayon A, Javoy-agid F, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. *Brain* 1991;114:1953-75. DOI PubMed
82. Lei P, Ayton S, Finkelstein DI, et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. *Nat Med* 2012;18:291-5. DOI PubMed
83. Oakley AE, Collingwood JF, Dobson J, et al. Individual dopaminergic neurons show raised iron levels in Parkinson disease. *Neurology* 2007;68:1820-5. DOI PubMed
84. Friedrich I, Reimann K, Jankuhn S, et al. Cell specific quantitative iron mapping on brain slices by immuno-μPIXE in healthy elderly and Parkinson's disease. *Acta Neuropathol Commun* 2021;9:47. DOI PubMed PMC
85. Martin-bastida A, Lao-kaim NP, Loane C, et al. Motor associations of iron accumulation in deep grey matter nuclei in Parkinson's disease: a cross-sectional study of iron-related magnetic resonance imaging susceptibility. *Eur J Neurol* 2017;24:357-65. DOI PubMed
86. Guan X, Xuan M, Gu Q, et al. Regionally progressive accumulation of iron in Parkinson's disease as measured by quantitative susceptibility mapping: *NMR Biomed* 2017;30:e3489. DOI PubMed PMC
87. Ayton S, Lei P. Nigral iron elevation is an invariable feature of Parkinson's disease and is a sufficient cause of neurodegeneration. *Biomed Res Int* 2014;2014:581256. DOI PubMed PMC
88. Lei P, Ayton S, Appukuttan AT, et al. Lithium suppression of tau induces brain iron accumulation and neurodegeneration. *Mol Psychiatry* 2017;22:396-406. DOI PubMed
89. Lei P, Ayton S, Bush AI. The essential elements of Alzheimer's disease. *J Biol Chem* 2021;296:100105. DOI PubMed PMC
90. Lei P, Ayton S, Moon S, et al. Motor and cognitive deficits in aged tau knockout mice in two background strains. *Mol Neurodegener* 2014;9:29. DOI PubMed PMC
91. Ayton S, Lei P, Hare DJ, et al. Parkinson's disease iron deposition caused by nitric oxide-induced loss of β-amyloid precursor protein. *J Neurosci* 2015;35:3591-7. DOI PubMed PMC
92. Han J, Fan Y, Wu P, et al. Parkinson's disease dementia: synergistic effects of alpha-synuclein, tau, beta-amyloid, and iron. *Front Aging Neurosci* 2021;13:743754. DOI PubMed PMC
93. Finkelstein DI, Billings JL, Adlard PA, et al. The novel compound PBT434 prevents iron mediated neurodegeneration and alpha-synuclein toxicity in multiple models of Parkinson's disease. *Acta Neuropathol Commun* 2017;5:53. DOI PubMed PMC
94. Ostrerova-Golts N, Petrucelli L, Hardy J, et al. The A53T alpha-synuclein mutation increases iron-dependent aggregation and toxicity. *J Neurosci* 2000;20:6048-54. DOI PubMed PMC
95. Friedlich AL, Tanzi RE, Rogers JT. The 5'-untranslated region of Parkinson's disease alpha-synuclein messengerRNA contains a predicted iron responsive element. *Mol Psychiatry* 2007;12:222-3. DOI PubMed
96. Rogers JT, Mikkilineni S, Cantuti-castelvetri I, et al. The alpha-synuclein 5'untranslated region targeted translation blockers: anti-alpha synuclein efficacy of cardiac glycosides and Posiphen. *J Neural Transm* 2011;118:493-507. DOI PubMed PMC
97. Wu J, Tuo Q, Lei P. Ferroptosis, a recent defined form of critical cell death in neurological disorders. *J Mol Neurosci* 2018;66:197-206. DOI PubMed
98. Zhou ZD, Tan E. Iron regulatory protein (IRP)-iron responsive element (IRE) signaling pathway in human neurodegenerative diseases. *Mol Neurodegener* 2017;12:75. DOI PubMed PMC
99. Yan H, Zou T, Tuo Q, et al. Ferroptosis: mechanisms and links with diseases. *Sig Transduct Target Ther* 2021;6:49. DOI PubMed PMC
100. Wang R, Wang Y, Qu L, et al. Iron-induced oxidative stress contributes to α-synuclein phosphorylation and up-regulation via polo-like kinase 2 and casein kinase 2. *Neurochem Int* 2019;125:127-35. DOI PubMed
101. Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antioxid Redox Signal* 2014;21:195-210. DOI PubMed PMC
102. Shukla JJ, Stefanova N, Bush AI, McColl G, Finkelstein DI, McAllum EJ. Therapeutic potential of iron modulating drugs in a mouse model of multiple system atrophy. *Neurobiol Dis* 2021;159:105509. DOI PubMed
103. Finkelstein DI, Shukla JJ, Cherny RA, et al. The compound ATH434 prevents alpha-synuclein toxicity in a murine model of multiple system atrophy. *J Parkinsons Dis* 2022;12:105-15. DOI PubMed PMC
104. Dauer Née Joppe K, Tatenhorst L, Caldi Gomes L, et al. Brain iron enrichment attenuates α-synuclein spreading after injection of preformed fibrils. *J Neurochem* 2021;159:554-73. DOI PubMed
105. McLeary FA, Rcom-H'cheo-Gauthier AN, Goulding M, et al. Switching on endogenous metal binding proteins in Parkinson's disease. *Cells* 2019;8:179. DOI PubMed PMC
106. Valiente-Gabioud AA, Torres-Monserrat V, Molina-Rubino L, Binolfi A, Griesinger C, Fernández CO. Structural basis behind the interaction of Zn^{2+} with the protein α-synuclein and the Aβ peptide: a comparative analysis. *J Inorg Biochem* 2012;117:334-41. DOI PubMed
107. Ranjan P, Ghosh D, Yarramala DS, Das S, Maji SK, Kumar A. Differential copper binding to alpha-synuclein and its disease-associated mutants affect the aggregation and amyloid formation. *Biochim Biophys Acta Gen Subj* 2017;1861:365-74. DOI PubMed

108. Li Y, Yu Y, Ma G. Modulation Effects of Fe^{3+}, Zn^{2+}, and Cu^{2+} Ions on the amyloid fibrillation of α-synuclein: insights from a FTIR investigation. *Molecules* 2022;27:8383. DOI PubMed PMC
109. Galvagnion C, Buell AK, Meisl G, et al. Lipid vesicles trigger α-synuclein aggregation by stimulating primary nucleation. *Nat Chem Biol* 2015;11:229-34. DOI PubMed PMC
110. Kiechle M, Grozdanov V, Danzer KM. The role of lipids in the initiation of α-synuclein misfolding. *Front Cell Dev Biol* 2020;8:562241. DOI PubMed PMC
111. Smeyne RJ, Noyce AJ, Byrne M, Savica R, Marras C. Infection and risk of Parkinson's disease. *J Parkinsons Dis* 2021;11:31-43. DOI PubMed PMC
112. Reish HE, Standaert DG. Role of α-synuclein in inducing innate and adaptive immunity in Parkinson disease. *J Parkinsons Dis* 2015;5:1-19. DOI PubMed PMC
113. Prigent A, Lionnet A, Durieu E, et al. Enteric alpha-synuclein expression is increased in Crohn's disease. *Acta Neuropathol* 2019;137:359-61. DOI
114. Kasen A, Houck C, Burmeister AR, Sha Q, Brundin L, Brundin P. Upregulation of α-synuclein following immune activation: possible trigger of Parkinson's disease. *Neurobiol Dis* 2022;166:105654. DOI PubMed
115. Kim C, Lv G, Lee JS, et al. Exposure to bacterial endotoxin generates a distinct strain of α-synuclein fibril. *Sci Rep* 2016;6:30891. DOI PubMed PMC
116. Tolosa E, Vila M, Klein C, Rascol O. LRRK2 in Parkinson disease: challenges of clinical trials. *Nat Rev Neurol* 2020;16:97-107. DOI PubMed
117. Kalia LV, Lang AE, Hazrati LN, et al. Clinical correlations with Lewy body pathology in LRRK2-related Parkinson disease. *JAMA Neurol* 2015;72:100-5. DOI PubMed PMC
118. Poulopoulos M, Cortes E, Vonsattel JP, et al. Clinical and pathological characteristics of LRRK2 G2019S patients with PD. *J Mol Neurosci* 2012;47:139-43. DOI PubMed PMC
119. Kim CY, Alcalay RN. Genetic forms of Parkinson's disease. *Semin Neurol* 2017;37:135-46. DOI PubMed
120. Nabli F, Ben Sassi S, Amouri R, Duda JE, Farrer MJ, Hentati F. Motor phenotype of LRRK2-associated Parkinson's disease: a Tunisian longitudinal study. *Mov Disord* 2015;30:253-8. DOI PubMed
121. Bieri G, Brahic M, Bousset L, et al. LRRK2 modifies α-syn pathology and spread in mouse models and human neurons. *Acta Neuropathol* 2019;137:961-80. DOI PubMed PMC
122. Obergasteiger J, Frapporti G, Lamonaca G, et al. Kinase inhibition of G2019S-LRRK2 enhances autolysosome formation and function to reduce endogenous alpha-synuclein intracellular inclusions. *Cell Death Discov* 2020;6:45. DOI PubMed PMC
123. Di Maio R, Hoffman EK, Rocha EM, et al. LRRK2 activation in idiopathic Parkinson's disease. *Sci Transl Med* 2018;10:eaar5429. DOI PubMed PMC
124. Kim C, Beilina A, Smith N, et al. LRRK2 mediates microglial neurotoxicity via NFATc2 in rodent models of synucleinopathies. *Sci Transl Med* 2020;12:eaay0399. DOI PubMed PMC
125. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392:605-8. DOI
126. Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive and motor function in long-duration PARKIN-associated Parkinson disease. *JAMA Neurol* 2014;71:62-7. DOI PubMed PMC
127. Li X, Gehring K. Structural studies of parkin and sacsin: mitochondrial dynamics in neurodegenerative diseases. *Mov Disord* 2015;30:1610-9. DOI PubMed
128. Pramstaller PP, Schlossmacher MG, Jacques TS, et al. Lewy body Parkinson's disease in a large pedigree with 77 parkin mutation carriers. *Ann Neurol* 2005;58:411-22. DOI PubMed
129. Seike N, Yokoseki A, Takeuchi R, et al. Genetic variations and neuropathologic features of patients with PRKN mutations. *Mov Disord* 2021;36:1634-43. DOI PubMed
130. Lo Bianco C, Schneider BL, Bauer M, et al. Lentiviral vector delivery of parkin prevents dopaminergic degeneration in an alpha-synuclein rat model of Parkinson's disease. *Proc Natl Acad Sci U S A* 2004;101:17510-5. DOI PubMed PMC
131. LaVoie MJ, Cortese GP, Ostaszewski BL, Schlossmacher MG. The effects of oxidative stress on parkin and other E3 ligases. *J Neurochem* 2007;103:2354-68. DOI PubMed
132. Rocha Cabrero F, Morrison EH. Lewy Bodies. In: StatPearls; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK536956/. [Last accessed on 27 Jun 2023].
133. Adler CH, Connor DJ, Hentz JG, et al. Incidental Lewy body disease: clinical comparison to a control cohort. *Mov Disord* 2010;25:642-6. DOI PubMed PMC
134. Chu Y, Kordower JH. Age-associated increases of alpha-synuclein in monkeys and humans are associated with nigrostriatal dopamine depletion: is this the target for Parkinson's disease? *Neurobiol Dis* 2007;25:134-49. DOI PubMed
135. Wilhelmus MMM, Chouchane O, Loos M, et al. Absence of tissue transglutaminase reduces amyloid-beta pathology in APP23 mice. *Neuropathol Appl Neurobiol* 2022;48:e12796. DOI PubMed PMC
136. Li X, Lei P, Tuo Q, et al. Enduring elevations of hippocampal amyloid precursor protein and iron are features of β-amyloid toxicity and are mediated by tau. *Neurotherapeutics* 2015;12:862-73. DOI PubMed PMC
137. Ghosh S, Ali R, Verma S. Aβ-oligomers: a potential therapeutic target for Alzheimer's disease. *Int J Biol Macromol* 2023;239:124231. DOI PubMed

138. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med* 2023;388:9-21. DOI PubMed
139. Alves F, Kalinowski P, Ayton S. Accelerated brain volume loss caused by anti-β-amyloid drugs: a systematic review and meta-analysis. *Neurology* 2023;100:e2114-24. DOI PubMed PMC
140. Lohmann E, Hanağası HA, Gürvit H, et al. The impact of familial structure on Parkinson's disease in istanbul medical school, turkey. *Int J Neurosci* 2012;122:102-5. DOI PubMed
141. Proukakis C, Dudzik CG, Brier T, et al. A novel α-synuclein missense mutation in Parkinson disease. *Neurology* 2013;80:1062-4. DOI PubMed PMC
142. Puschmann A, Jiménez-Ferrer I, Lundblad-Andersson E, et al. Low prevalence of known pathogenic mutations in dominant PD genes: a Swedish multicenter study. *Parkinsonism Relat Disord* 2019;66:158-65. DOI PubMed
143. Tan LY, Tang KH, Lim LYY, Ong JX, Park H, Jung S. α-Synuclein at the presynaptic axon terminal as a double-edged sword. *Biomolecules* 2022;12:507. DOI PubMed PMC
144. Bozi M, Papadimitriou D, Antonellou R, et al. Genetic assessment of familial and early-onset Parkinson's disease in a Greek population. *Eur J Neurol* 2014;21:963-8. DOI PubMed
145. Papadimitriou D, Antonelou R, Miligkos M, et al. Motor and nonmotor features of carriers of the p.A53T alpha-synuclein mutation: a longitudinal study. *Mov Disord* 2016;31:1226-30. DOI PubMed
146. Markopoulou K, Dickson DW, McComb RD, et al. Clinical, neuropathological and genotypic variability in SNCA A53T familial Parkinson's disease. Variability in familial Parkinson's disease. *Acta Neuropathol* 2008;116:25-35. DOI PubMed PMC
147. Goldwurm S, Di Fonzo A, Simons EJ, et al. The G6055A (G2019S) mutation in LRRK2 is frequent in both early and late onset Parkinson's disease and originates from a common ancestor. *J Med Genet* 2005;42:e65. DOI PubMed PMC
148. Aasly JO, Toft M, Fernandez-Mata I, et al. Clinical features of LRRK2-associated Parkinson's disease in central Norway. *Ann Neurol* 2005;57:762-5. DOI PubMed
149. Lin CH, Chen PL, Tai CH, et al. A clinical and genetic study of early-onset and familial parkinsonism in taiwan: an integrated approach combining gene dosage analysis and next-generation sequencing. *Mov Disord* 2019;34:506-15. DOI PubMed PMC
150. Samaranch L, Lorenzo-Betancor O, Arbelo JM, et al. PINK1-linked parkinsonism is associated with Lewy body pathology. *Brain* 2010;133:1128-42. DOI PubMed
151. Ishihara-Paul L, Hulihan MM, Kachergus J, et al. PINK1 mutations and parkinsonism. *Neurology* 2008;71:896-902. DOI PubMed PMC
152. Tan AH, Lohmann K, Tay YW, et al. PINK1 p.Leu347Pro mutations in Malays: prevalence and illustrative cases. *Parkinsonism Relat Disord* 2020;79:34-9. DOI PubMed
153. Kasten M, Weichert C, Lohmann K, Klein C. Clinical and demographic characteristics of PINK1 mutation carriers - a meta-analysis. *Mov Disord* 2010;25:952-4. DOI PubMed
154. Ephraty L, Porat O, Israeli D, et al. Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to PINK1 mutations. *Mov Disord* 2007;22:566-9. DOI PubMed
155. Takanashi M, Li Y, Hattori N. Absence of Lewy pathology associated with PINK1 homozygous mutation. *Neurology* 2016;86:2212-3. DOI PubMed
156. Nybø CJ, Gustavsson EK, Farrer MJ, Aasly JO. Neuropathological findings in PINK1-associated Parkinson's disease. *Parkinsonism Relat Disord* 2020;78:105-8. DOI PubMed
157. Castelo Rueda MP, Raftopoulou A, Gögele M, et al. Frequency of heterozygous parkin (PRKN) variants and penetrance of Parkinson's disease risk markers in the population-based CHRIS cohort. *Front Neurol* 2021;12:706145. DOI PubMed PMC
158. Hedrich K, Djarmati A, Schäfer N, et al. DJ-1 (PARK7) mutations are less frequent than parkin (PARK2) mutations in early-onset Parkinson disease. *Neurology* 2004;62:389-94. DOI PubMed
159. Aharon-Peretz J, Badarny S, Rosenbaum H, Gershoni-Baruch R. Mutations in the glucocerebrosidase gene and Parkinson disease: phenotype-genotype correlation. *Neurology* 2005;65:1460-1. DOI PubMed
160. Brockmann K, Srulijes K, Hauser AK, et al. GBA-associated PD presents with nonmotor characteristics. *Neurology* 2011;77:276-80. DOI PubMed
161. Ren J, Zhang R, Pan C, et al. Prevalence and genotype-phenotype correlations of GBA-related Parkinson disease in a large Chinese cohort. *Eur J Neurol* 2022;29:1017-24. DOI PubMed PMC
162. Clark LN, Kartsaklis LA, Wolf Gilbert R, et al. Association of glucocerebrosidase mutations with dementia with Lewy bodies. *Arch Neurol* 2009;66:578-83. DOI PubMed PMC
163. Neumann J, Bras J, Deas E, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain* 2009;132:1783-94. DOI PubMed PMC