**PARK Genes Link Mitochondrial Dysfunction and Alpha-Synuclein Pathology in Sporadic Parkinson’s Disease**

Wen Li<sup>1,2</sup>, YuHong Fu<sup>1,3</sup>, Glenda M. Halliday<sup>1,3</sup> and Carolyn M. Sue<sup>1,2*</sup>

<sup>1</sup> Brain and Mind Centre, University of Sydney, Sydney, NSW, Australia; <sup>2</sup> Kolling Institute of Medical Research, Faculty of Medicine and Health, University of Sydney, Royal North Shore Hospital, St Leonards, NSW, Australia; <sup>3</sup> School of Medical Science, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Parkinson’s disease (PD) is an age-related neurodegenerative disorder affecting millions of people worldwide. The disease is characterized by the progressive loss of dopaminergic neurons and spread of Lewy pathology (α-synuclein aggregates) in the brain but the pathogenesis remains elusive. PD presents substantial clinical and genetic variability. Although its complex etiology and pathogenesis has hampered the breakthrough in targeting disease modification, recent genetic tools advanced our approaches. As such, mitochondrial dysfunction has been identified as a major pathogenic hub for both familial and sporadic PD. In this review, we summarize the effect of mutations in 11 PARK genes (SNCA, PRKN, PINK1, DJ-1, LRRK2, ATP13A2, PLA2G6, FBXO7, VPS35, CHCHD2, and VPS13C) on mitochondrial function as well as their relevance in the formation of Lewy pathology. Overall, these genes play key roles in mitochondrial homeostatic control (biogenesis and mitophagy) and functions (e.g., energy production and oxidative stress), which may crosstalk with the autophagy pathway, induce proinflammatory immune responses, and increase oxidative stress that facilitate the aggregation of α-synuclein. Thus, rectifying mitochondrial dysregulation represents a promising therapeutic approach for neuroprotection in PD.

**Keywords:** Parkinson’s disease, mitochondria, mitophagy, α-synuclein pathology, PARK genes

**INTRODUCTION**

Parkinson’s disease (PD) is an age-related neurodegenerative disorder with an insidious onset and a substantial preclinical phase (estimated as > 20 years). The progressive aggregation of α-synuclein (Lewy pathology) through the brain and the loss of midbrain dopamine neurons are the pathological landmarks of PD (Surmeier et al., 2017; Fares et al., 2021). Although the etiology of PD is multifactorial, mitochondrial dysfunction has been recognized as a main neuropathogenic mechanism that can affect energy provision and biological pathways (e.g., autophagy, proinflammatory, and antioxidant) to potentially facilitate the Lewy pathology and neuronal loss (Poewe et al., 2017; Park et al., 2018; Grunewald et al., 2019; Pang et al., 2019; Fenton et al., 2021; Onishi et al., 2021).
High-throughput next-generation sequencing and genome-wide association studies have revealed PD risk-associated genes, including 23 PARK genes (Schulte and Gasser, 2011; Marras et al., 2017; Poewe et al., 2017) and others (e.g., HLA-DRA, EIF4G1, GBA, MAPT, BST1, TMEM230, APOE, and POLG). Most PARK genes have been revealed as low prevalence (Tran et al., 2020), perhaps a reason of limited research on their involvement in sporadic PD. We reviewed 11 PARK genes (Table 1) relevant to mitochondrial function, aiming to highlight their potential roles in the etiology of sporadic PD.

**PARK GENES IN MITOCHONDRIAL FUNCTION AND HOMEOSTATIC CONTROL**

**PARK1/4 (SNCA): α-Synuclein**

SNCA was the first PARK gene discovered to cause PD (Polymeropoulos et al., 1996). The prevalence of SNCA mutations is estimated as ~0.05% in a cohort size of more than 2,000 sporadic PD patients (Tan et al., 2019). SNCA mutations can cause early-onset PD of variable clinical phenotypes and diverse Lewy pathologies (Campelo and Silva, 2017). Duplications or triplications of SNCA cause gene dosage effect on PD severity (Ibanez et al., 2004; Miller et al., 2004).

The physiological function of α-synuclein is not fully understood. Consistent with its many functions, this native disordered protein locates in multiple cellular organelles and sites: mitochondria, nucleus, synapse, endoplasmic reticulum (ER), Golgi, and lysosomes (Bernal-Conde et al., 2019; Shahmoradian et al., 2019).

α-Synuclein directly and indirectly interacts with mitochondria (Ganguly et al., 2018; Grunewald et al., 2019). It maintains mitochondrial membrane composition and structure and its deposition in neurons alters mitochondrial morphology and fragmentation, membrane potential, respiratory chain complex I function, and increases oxidative stress (Di Maio et al., 2016; Zambon et al., 2019; Hannestad et al., 2020).

Overexpression of mitochondria-targeted α-synuclein results in mitochondrial reactive oxygen species (ROS) formation, reduced ATP levels, and neuronal death (Ganjam et al., 2019). Vice versa, mitochondrial dysfunction causes α-synuclein pathology as shown in traditional PD models induced by paraquat and rotenone. In addition, α-synuclein interacts with a number of critical mitochondrial proteins, including voltage-dependent anion-selective channel 1, PINK1, Parkin, and DJ-1 proteins (Bernal-Conde et al., 2019). It is also associated with mitochondrial Sirtuin 3, a nicotinamide adenine dinucleotide (NAD+)-dependent enzyme critical in mitochondrial quality control and the prevention of oxidative stress (Park et al., 2020).

**PARK2 (PRKN): Parkin RBR E3 Ubiquitin Protein Ligase (parkin)**

PRKN, the second identified PD gene (Matsumine et al., 1997) is the most common autosomal recessive gene causing early onset PD (Klein and Lohmann-Hedrich, 2007; Jiang et al., 2020). There are over 100 known mutations in PRKN that lead to either a dysfunctional small Parkin protein being rapidly degraded or defective parkin without activity (Abbas et al., 1999). Some, but not all PRKN mutations cases have Lewy Pathology (Farrer et al., 2001; Shimura et al., 2001; Pramstaller et al., 2005; Miyakawa et al., 2013; Johansen et al., 2018).

Parkin is a HECT/RING hybrid ligase that receives ubiquitin on its catalytic center and passes ubiquitin onto its substrates (Trempe et al., 2013). It regulates mitochondrial quality control through mitophagy and mitochondrial biogenesis. A loss of Parkin function contributes to the pathogenesis of PD through affecting mitochondria, innate immunity, and interactions with α-synuclein. In human cell models, the lack of parkin altered mitochondrial respiratory chain function, oxidative stress levels, mitochondrial morphology and motility, mitophagy (Koentjoro et al., 2017; Bonello et al., 2019), and mitochondrial biogenesis [by upregulating PARIS and subsequently downregulating PGC-1α (Kumar et al., 2020)]. Notably, loss of Parkin alone is not sufficient to induce dopaminergic (DA) neuron loss or motor deficits in mouse models (Aguiar Jr., Tristao et al., 2013). However, in combination with a POLG mutation (a proofreading-defective mtDNA polymerase), Parkin-deficient mice have both DA neuron loss and motor defects (Sliter et al., 2018).

**PARK6 (PINK1): PTEN Induced Kinase 1 (PINK1)**

PINK1 is the second most common autosomal recessive gene for PD identified in 2004 (Valente et al., 2004). Heterozygous pathogenic mutations were found in both sporadic and familial PD (Klein et al., 2007). More than 70 mutations have been identified in PINK1 (Siuda et al., 2014; Puschmann et al., 2017). Heterozygous G411S mutation cells have normal PINK1 levels but reduced kinase activity, altered ubiquitin phosphorylation, parkin recruitment, and mitophagy, whereas heterozygous Q456X mutation cells have reduced levels of PINK1 with decreased kinase activity, but their mitochondrial response to damage remains intact (Puschmann et al., 2017). Most but not all PINK1 mutation cases have Lewy pathology, gliosis, and DA neuronal loss in the substantia nigra (Samaranch et al., 2010; Takanashi et al., 2016; Nybo et al., 2020).

PINK1 is a mitochondrial serine/threonine-protein kinase that recruits parkin to depolarized mitochondria for mitophagy (Matsuda et al., 2013). PINK1-deficient mice show significantly impaired mitochondrial respiration in the brain with aging, but no altered mitochondrial morphology, DA neuron loss, or Lewy pathology (Kitada et al., 2007; Gautier et al., 2008). Interestingly, PINK1-deficient rats exhibit DA neuron loss, altered neurotransmitters, and Lewy pathology at 12 months (Creed and Goldberg, 2018, 2020; Creed et al., 2019). Although PINK1/parkin are essential in the mitophagy pathway, they are not required in basal mitophagy (McWilliams et al., 2018). PINK1/parkin are significantly involved in regulating the basal inflammatory response (Sliter et al., 2018; Wang et al., 2019). Human cell models that lack PINK1 have altered mitochondrial...
Autosomal recessive inheritance

| Locus | Genes | Mutation | No. of cases reported | Mean age at onset | Disease progression/ disease duration | Initial signs and symptoms (Top 5 whenever available) | L-Dopa response (out of PD patient tested) | α-synuclein pathology | Brain region M vs Y Up-regulated (≥ 2 folds) | Brain region M vs Y Down-regulated (≥ 2 folds) |
|-------|-------|----------|----------------------|------------------|--------------------------------------|----------------------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| PARK1/PARK4 | SNCA | Missense (A30P, E46K, H50Q, G51D, A53E, A53T, A32V) or multiplication | 146 | 40s | Rapid (< 10 years) | Bradykinesia; Rigidty; Depression | Good (50/103) | Yes | ATZ, BLa, Pu | BMA, 10, RaM |
| PARK8 | LRRK2 | Missense (R1441G, Y1669C, G2019S, I2220T, G2388) or gain of function | 724 | 50s | Rapid (15–20 years) | Tremor; Bradykinesia; Rigidity | Good (276/476) | Yes | CgGf, 10, RaM, LC, RpH, FuG | ATZ, BLa, BMA, Dt, CgGr, RpH, Acb, VT |
| PARK17 | VPS35 | Missense (D620N) | 67 | 50s | Slow | Bradykinesia; Postural instability; Rigidity | Good (8/45) | Yes | BLa, Pu | BMA, PrG, RpH, FuG |

Autosomal dominant inheritance

| Locus | Genes | Mutation | No. of cases reported | Mean age at onset | Disease progression/ disease duration | Initial signs and symptoms (Top 5 whenever available) | L-Dopa response (out of PD patient tested) | α-synuclein pathology | Brain region M vs Y Up-regulated (≥ 2 folds) | Brain region M vs Y Down-regulated (≥ 2 folds) |
|-------|-------|----------|----------------------|------------------|--------------------------------------|----------------------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| PARK2 | PARK7 | Missense (K161N, R256C, T415N, T415N, 202–203 delA>G, 255delA and 321–322insGT, W453STOP), multiplication, deletion, or loss of function | 1,000 | 30s | Slow (27–50) | Tremor; Bradykinesia; Dystonia; Tremor at rest; Rigidity | Good (192/427) | Yes | Dt, CA4 | ATZ, BMA, CgGr, SN, 10, RaM, RpH, Pu, Vt |
| PARK6 | PINK1 | Missense (G411S, Q456X), deletion, or loss of function | 151 | 30s | Median (6–28) | Tremor; Bradykinesia; Rigidity; Dystonia | Good (84/113) | Yes | Dt, CA4 | ATZ, BMA, CgGr, SN, 10, RaM, RpH, Pu, Vt |
| PARK7 | DJ1 | Missense (A104T, M26I, L10P, L186P, L172Q, and P159DEL) or loss of function | 33 | 20s | Slow | Bradykinesia; Dystonia; Tremor | Good (5/25) | Yes | Crus II, CgGf, SN | BMA, CgGr, 10, RaM, RpH, Acb |

Atypical Parkinsonism

| Locus | Genes | Mutation | No. of cases reported | Mean age at onset | Disease progression/ disease duration | Initial signs and symptoms (Top 5 whenever available) | L-Dopa response (out of PD patient tested) | α-synuclein pathology | Brain region M vs Y Up-regulated (≥ 2 folds) | Brain region M vs Y Down-regulated (≥ 2 folds) |
|-------|-------|----------|----------------------|------------------|--------------------------------------|----------------------------------------------------------|-------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|
| PARK9 | ATP13A2 | Missense (F182L, G504R, G877R, T112M, G333R, A746T), or loss of function | 36 | 10s | Slow | Bradykinesia; Intellectual development disorder; Cognitive decline; Gait difficulties; Rigidity | Good (9/30) | Yes (in vitro) | ATZ, BLa, BMA, CA4, Vt | CgGf, CgGr, SPl, FuG, STG |
| PARK14 | PLA2G6 | Missense (G31A, D331Y/M3581IfsX) or loss of function | 7 | 20–30s | Rapid (1–15) | Bradykinesia; Spasticity; Hyperreflexia | Moderate | Yes | CgGf, CA2, SPl, Acb, Pu, FuG, STG | BMA, Dt, VTa, RaM, RpH |
| PARK15 | FBXO7 | Missense (R378Q, R498X, and T222M) | 26 | 10–20s | Rapid | Bradykinesia; Tremor; Gait difficulties; Rigidity; Behavioral abnormalities | Good (6/18) | Yes | CgGf | 10, SPl, Pu, STG |
| PARK22 | CHCHD2 | Missense (T61P) | 19 | 50s | Long | Bradykinesia; Postural instability; Depression | Good | Yes | Dt, VTa, LC | BMA, PrG, 10, SPl, Pu, FuG, STG |
| PARK23 | VPS13C | Missense (A269S, W396C, A444P, G1389R, Q1593L, and E3109STOP) or deletion (452–930Del) | 4 | 20–30s | Rapid | Bradykinesia; Rigidty; Dystonia; Depression | Moderate | Yes | CgGf, VTa, LC | CgGr, SPl, RpH, Acb |

Information for SNCA, LRRK2, VPS35, PINK1, DJ1, ATP13A2, PLA2G6, FBXO7, and VPS13C in this table were extracted from MDS gene, International Parkinson and Movement Disorder Society (http://mndgene.org). MDSgene currently collects data on 1651 different mutations in 6628 movement disorder patients extracted from 1250 publications (Klein et al., 2018). Information for PLA2G6 and CHCHD2 gene extracted from Online mendelian Inheritance in Man (http://omim.org). Mutations were shown to affect mitochondria function. Mutations were shown to involve in the formation of α-synuclein pathology. Abbreviations: Y-Young age (age of 24, 31, and 39), M-Middle age (age of 49, 55, and 57). M vs Y up-regulated: up-regulated gene expression with a fold change of greater or equal to 2. M vs Y down-regulated: down-regulated genes expression with a fold change of greater or equal to 2 (M vs Y).
respiratory chain function, morphology, motility, and mitophagy [reviewed in Grunewald et al. (2019)].

**PARK7 (DJ-1): Parkinsonism Associated Deglycase (DJ-1)**

Mutations in DJ-1 were identified as a rare cause of early onset recessive PD in 2003 (Bonifati et al., 2003). Around 20 pathogenic DJ-1 mutations have been identified with reduced protein due to rapid degradation (Ramsey and Giasson, 2010), and less dimerization into its functional form (Kumar et al., 2019). The autopsy of a patient with L172Q mutation showed severe DA neuronal loss in the substantia nigra with Lewy pathology (Taipa et al., 2016). About 57% of DJ-1 mutation carriers exhibit non-motor symptoms, a higher proportion than PRKN or PINK1 mutation carriers (Kasten et al., 2018).

DJ-1 is involved in cellular transformation, oxidative stress response, and mitochondrial function (Di Nottia et al., 2017; Raininga et al., 2017). DJ-1 responds to oxidative stress by accumulating on the outer mitochondrial membrane (OMM) in a PINK1/parkin dependent manner (Thomas et al., 2011; Joselin et al., 2012) which may be neuroprotective (Piston et al., 2017). Depletion of DJ-1 leads to increased ROS, decreased mitochondrial membrane potential, and accumulation of dysfunctional mitochondria, which can be rescued by increasing parkin (Andres-Mateos et al., 2007; Trempe and Fon, 2013; Ozawa et al., 2020). DJ-1 directly interacts with α-synuclein monomers and oligomers in mouse brains (Zondler et al., 2014) and DJ-1 deficiency increases α-synuclein aggregation in human and mouse models (Shendelman et al., 2004; Xu et al., 2017). Notably, the loss of DJ-1 does not induce nigral DA neuron demise in mice (Goldberg et al., 2005). Dj-1-deficient rats show DA neuron loss and evident motor abnormalities (Dave et al., 2014). Similar to SNCA, LRRK2, and UCHL1, mutations in DJ-1 block or reduce the activity of chaperone-mediated autophagy (Sala et al., 2016).

**PARK8 (LRRK2): Leucine-Rich Repeat Kinase 2 (LRRK2)**

LRRK2, discovered in 2004, is the most frequent autosomal dominant gene causing PD with more than 100 mutations (Paisan-Ruiz et al., 2004; Rui et al., 2018). Genome Aggregation Database predicts LOF in LRRK2 variants cause an 82.5% reduction in protein level, with no change in lifespan or clinical phenotype (Whiffin et al., 2020). LRRK2 mutations generally develop later in life and are clinically similar to sporadic PD, although up to 50% do not have Lewy pathology. Mouse models studying G2019S, R1441G, and Lrrk2-deficient failed to show correlation between loss of function (LOF) of LRRK2 and α-synuclein pathology (Daher et al., 2012; Xiong et al., 2017) but impaired parkin-mediated mitophagy is found in fibroblasts from patients with the G2019S mutation (Bonello et al., 2019).

LRRK2 has multiple domains including a kinase and GTPase enzyme. It is involved in a wide range of cellular processes (Berwick et al., 2019; Marchand et al., 2020) and interacts with Miro on OMM to promote its removal, stopping mitochondrial motility and initiating mitophagy (Hsieh et al., 2016). RAB10, a substrate of LRRK2 kinase activity, accumulates on depolarized mitochondria and interacts with the autophagy receptor OPTN (optineurin) to mediate mitophagy in a PINK1/parkin-dependent manner (Wauters et al., 2020). The toxic gain in function of LRRK2 kinase activity inhibits the accumulation of RAB10 on mitochondria (Wauters et al., 2020). The lack of LRRK2 in macrophages induces oxidative stress and dynamin-related protein 1 (DRP1)-dependent mitochondrial fragmentation (Weindel et al., 2020).

**PARK9 (ATP13A2): ATPase Cation Transporting 13A2 (ATP13A2)**

Loss of function of ATP13A2 was initially reported in Kufor-Rakeb syndrome (KRS; Ramirez et al., 2006) and in three other distinct neurodegenerative conditions: juvenile-onset neuronal ceroid lipofuscinosis (Bras et al., 2012), juvenile-onset hereditary spastic paraplegia (Estrada-Cuzcano et al., 2017), and amyotrophic lateral sclerosis-like phenotype (Spataro et al., 2019). More than 30 mutations have been identified in ATP13A2 and rare variants may contribute to PD risk (Cristina et al., 2020). Mutations in ATP13A2 cause decreased protein stability, increased proteasomal degradation, impaired polyanime transport and accumulation in lysosomes, and cell death (Podhajska et al., 2012; van Veen et al., 2020).

ATP13A2 is a lysosomal protein, located in the ER, endosomal and lysosomal membranes of neurons (de Tezanos Pinto and Adamo, 2018; Spataro et al., 2019). Loss of ATP13A2 in mouse and human cell models increase mitochondrial fragmentation and increase ROS and cell death (Gusdon et al., 2012; Park et al., 2014). Cell models from KRS patients and cells with silenced ATP13A2 show α-synuclein oxidation and accumulation (Tsunemi and Krainc, 2014). Over-expression of ATP13A2 reduces intracellular α-synuclein via the release of exosomes (Kong et al., 2014).

**PARK14 (PLA2G6): Phospholipase A2 Group VI (PLA2G6)**

PLA2G6 mutations was discovered in a large family with neurodegeneration in 2006 (Morgan et al., 2006). Mutations in PLA2G6 can cause autosomal recessive PD with high clinical variability, but all show cerebral and cerebellar atrophy, iron accumulation in the basal ganglia, cognitive decline (Khateeb et al., 2006; Ferese et al., 2018) and marked Lewy pathology (Paisan-Ruiz et al., 2012). A total of 16 mutations have been reported. Although most mutations of this gene are homozygous, a heterozygous missense mutation (G31A) has been reported to increase the risk of PD (Ferese et al., 2018). In contrast, compound heterozygous mutations (D331Y/M358IfsX) cause dystonia-parkinsonism with a poor response to levodopa (Chu et al., 2020).

PLA2G6, a calcium-independent phospholipase A2, is involved in maintaining mitochondrial function (Chiu et al., 2017). Overexpression of PLA2G6 exerted neuroprotection in human cells by increasing the level of mitophagy proteins in response to rotenone (Chiu et al., 2017). The loss of PLA2G6 results in shortened acyl-chains in phospholipids, which affects
FIGURE 1 | Interaction of proteins encoded by mitochondrial-related PARK genes. (A) Gene expression data was obtained from Allen Brain Atlas, Allen Institute. \( n = 2–3 / \text{group}. \) Y-Young (age of 24, 31, and 39), M-Middle age (age of 49, 55, and 57). Heatmap showing the z-score was generated using online Heatmap program (Babicki et al., 2016). Red boxes indicates up-regulated gene expression with a fold change of greater or equal to 2 (M vs Y) and green boxes indicates down-regulated genes expression with a fold change of greater or equal to 2 (M vs Y). (B) 3D heatmap of the 11 genes from Allen Brain Atlas, Allen Institute. Young (age of 24) and mid-age (age of 57); (C) The interactive pathways of proteins encoded by the 11 PARK genes generated from IPA (Ingenuity Systems Inc., Redwood city, CA, United States). Symbols are used to show mitochondrial function: *Morphology; #Fission/Fusion; ^Mitophagy; !ATP synthesis; and &ROS. (D) Top 35
ER homeostasis, neurotransmission, and promotes α-synuclein aggregation (Mori et al., 2019). Elevated expression of α-synuclein in neuronal mitochondria is observed in PLA2G6 deficiency (Sumi-Akamaru et al., 2016).

PARK15 (FBXO7): F-Box Protein 7 (FBXO7)
A homozygous mutation in FBXO7 was reported to cause autosomal recessive PD (Shojae et al., 2008). Mutations in FBXO7 have not been detected in sporadic PD (Conedera et al., 2016). Mutations in FBXO7 promote the aggregation of the toxic form of this protein in mitochondria, resulting in impairment of mitophagy and the ubiquitin-proteasome system (Zhou et al., 2015). Mutations in FBXO7 are increased in PD (Zhou et al., 2016). Mutations in FBXO7 recruit parkin into damaged mitochondria and facilitates its aggregation, but overexpression of FBXO7 can still rescue DA neuron degeneration in parkin null Drosophila (Burchell et al., 2013; Zhou et al., 2016) and restore PD phenotype in the absence of parkin, indicating FBXO7 mediates neuroprotective effects via a parkin-independent pathway (Burchell et al., 2013). Both soluble and insoluble FBXO7 are increased in PD (Zhou et al., 2015). FBXO7 immunoreactivity is detected in most α-synuclein aggregates in PD and in glial cytoplasmic inclusions of multiple system atrophy (Zhao et al., 2013). In contrast, only occasional tau-positive inclusions in Alzheimer’s disease and progressive supranuclear palsy contain FBXO7.

PARK17 (VPS35): Vacuolar Protein Sorting 35 Ortholog (VPS35)
Mutations in VPS35 were identified in 2008 (Wider et al., 2008) and are reported in patients with autosomal dominant PD. A heterozygous missense mutation D620N has been confirmed as pathogenic (Williams et al., 2017; Chen et al., 2019) and has been found in 0.056–0.91% of the sporadic PD patients (Ando et al., 2012; Kumar et al., 2012). The D620N mutation did not affect the stability, assembly, or subcellular location of the retromer (Tian et al., 2015), instead it enhanced LRRK2 kinase activity (Mir et al., 2018). D620N mutant mice show no motor disorders but have increased mitochondrial fission and fragmentation (Wang et al., 2017; Cataldi et al., 2018). VPS35 forms part of a retromer cargo-recognition complex involved in intracellular retrograde transport from endosomes to the trans-Golgi network (Hierro et al., 2007; Tabuchi et al., 2010). Loss of iPLA2-VIA (the Drosophila homolog of human PLAG2A) destabilizes VPS35 and impairs retromer function, resulting in ceramide accumulation and cell stress (Lin et al., 2018). VPS35 is implicated in the formation of mitochondria-derived vesicles directed to the peroxisome or lysosome for degradation of mitochondria proteins (Braschi et al., 2010; Wang et al., 2016). Lack of VPS35 in human cells with VPS35 mutations exhibit defective mitochondrial fusion and increased mitochondrial fragmentation (Tang et al., 2015). Mitochondrial dysfunction induced by VPS35 mutation can be restored by inhibition of mitochondrial fission (Wang et al., 2016). α-Synuclein is transported by the retromer complex (Miura et al., 2014). Heterozygous Vps35 KO mice show α-synuclein aggregation, DA neuron degeneration, impaired locomotor behavior, and altered lysosomal morphology (Tang et al., 2015). Overexpression of VPS35 reduces α-synuclein accumulation in mice overexpressing α-synuclein (Dhungel et al., 2015). Moreover, knockdown Vps35 in Drosophila results in α-synuclein accumulation (Miura et al., 2014).

PARK22 (CHCHD2): Coiled-Coil-Helix-Coiled-Coil-Helix Domain Containing 2 (CHCHD2)
Mutations in CHCHD2 are a rare cause of autosomal dominant PD, originally found in 3/340 PD patients in 2015 (Funayama et al., 2015). To date, there is only one brain autopsy of a PD patient carrying CHCHD2 T61I mutation that revealed widespread Lewy pathology with additional amyloid plaques and neurofibrillary tangles in the brainstem, limbic regions, and neocortex (Ikeda et al., 2019). α-Synuclein aggregation was accelerated by CHCHD2 T61I in human cells and in Drosophila. Human cells from T61I patients show accumulated CHCHD2 in the mitochondrial intermembrane space (IMS), resulting in increased ROS and apoptosis (Cornelissen et al., 2020). CHCHD2 (also called mitochondria nuclear retrograde regulator 1) contains at least one CHCH domain (Modjtahedi et al., 2016). The protein locates in the IMS (Aras et al., 2015). Loss of CHCHD2 function causes an abnormal mitochondrial matrix structure and impaired oxygen respiration in mitochondria resulting in oxidative stress, DA neuron loss, and motor dysfunction with aging (Meng et al., 2017). Importantly, overexpression of CHCHD2 rescues the phenotype of PD. In addition, CHCHD2 binds to cytochrome c and Bax inhibitor-1, suggesting the role CHCHD2 in regulating apoptosis and cell death (Liu et al., 2015). In Drosophila, CHCHD2 interacts with the Coiled-Coil-Helix-Coiled-Coil-Helix domain and facilitates its aggregation.
with the mitochondrial protein P32 and indirectly regulates the level of mitochondrial fusion protein, Opal, highlighting the role of CHCHD2 in regulating mitochondrial fusion and cristae morphology (Liu et al., 2015). Moreover, human cells lacking CHCHD2 have altered mitochondrial respiration (Harjuhaaho et al., 2020).

**PARK23 (VPS13C): Vacuolar Protein Sorting-Associate Protein 13C**

Mutations in VPS13C, identified in 2016 cause an autosomal recessive early onset PD, characterized by early cognitive decline and rapid disease progression (Lesage et al., 2016; Schormair et al., 2018). The post-mortem examination of the brain of the affected patient displayed reduced protein levels of VSP13C and the presence of α-synuclein pathology (Lesage et al., 2016; Smolders et al., 2021).

VPS13C acts at membrane contact sites on multiple organelles such as endosomes, mitochondria, and late endosomes and lysosomes for lipid delivery, which is important for mitochondrial biogenesis and function (Kumar et al., 2018). VPS13C was localized to the OMM as shown in HEK293 cells (Lesage et al., 2016) and was found between lipid droplets and mitochondria (Ramseyer et al., 2018). LOF in VPS13C in COS-7 monkey cells resulted in abnormal mitochondrial morphology, increased vulnerability to stress, and the activation of PINK1/parkin-dependent mitophagy (Lesage et al., 2016). Overexpression of W395C or A444P VPS13C in Hela or SH-SY5Y cells showed the ER-endosomal/lysosomal localization of VPS13C was lost, suggesting these mutants might affect the stability of the protein thereby influencing its localization (Smolders et al., 2021).

**DISCUSSION**

Over the past 20 years, great progress has been in our understanding of PD with the identification of 23 PARK genes. No doubt there will be more that await discovery. The frontiers in cell and developmental biology with the identification of 23 PARK genes highlighted here collectively emphasize the pathobiology of PD. These genes are involved in multiple stages of disease progression, from the initiation of mitochondrial damage to loss of DA neurons.

**REFERENCES**

Abbas, N., Lucking, C. B., Ricard, S., Durr, A., Bonifati, V., De Michele, G., et al. (1999). A wide variety of mutations in the parkin gene are responsible for autosomal recessive parkinsonism in Europe. French Parkinson's Disease Genetics Study Group and the European Consortium on Genetic Susceptibility in Parkinson's Disease. *Hum. Mol. Genet.* 8, 567–574. doi: 10.1093/hmg/8.4.567

Aguiar, A. S. Jr., Tristao, F. S., Amar, M., Chevarin, C., Lanfumey, L., Mongeau, R., et al. (2013). Parkin-knockout mice did not display increased vulnerability to intranasal administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Neurotox. Res.* 24, 280–287. doi: 10.1007/s12640-013-9389-0

Ando, M., Funayama, M., Li, Y., Kashihara, K., Murakami, Y., Ishizu, N., et al. (2012). VPS35 mutation in Japanese patients with typical Parkinson’s disease. *Mov. Disord.* 27, 1413–1417. doi: 10.1002/mds.25145

Andres-Mateos, E., Perier, C., Zhang, L., Blanchard-Fillion, B., Greco, T. M., Thomas, B., et al. (2007). DJ-1 gene deletion reveals that DJ-1 is an atypical peroxiredoxin-like peroxidase. *Proc. Natl. Acad. Sci. U.S.A.* 104, 14807–14812. doi: 10.1073/pnas.0703219104

**AUTHOR CONTRIBUTIONS**

WL and YF conceived of the presented data. WL and YF wrote the manuscript in consultation with GH and CS. GH and CS were in charge of overall direction and planning. All authors contributed to the article and approved the submitted version.

**FUNDING**

This work was supported by National Health and Medical Research Council (NHMRC) to CS and YF (#1141064) and funding to ForeFront, a collaborative research group at the Brain and Mind Centre University of Sydney, from NHMRC program (#1132524) and Dementia Team (#1095127) grants. GH is an NHMRC Leadership Fellow (#1176607). CS is an MRFF NHMRC Practitioner Fellow (#1136800).

**ACKNOWLEDGMENTS**

We thank the Allen Institute for Brain Science for providing transcriptomic data from donors, MDS gene, International Parkinson and Movement Disorder Society and Online Mendelian Inheritance in Man® for genetic data and relevant clinical data.
Chu, Y. T., Lin, H. Y., Chen, P. L., and Lin, C. H. (2020). Genotype-phenotype correlations of adult-onset PLA2G6-associated Neurodegeneration: case series and literature review. BMC Neurosci. 20:101. doi: 10.1186/s12883-019-1084-6

Conedera, S., Apaydin, H., Li, Y., Yoshino, H., Ikeda, A., Matsushima, T., et al. (2016). FBXO7 mutations in Parkinson's disease and multiple system atrophy. Neurobiol. Aging 40, 192.e191–192.e195.

Creed, R. B., and Goldberg, M. S. (2018). Analysis of alpha-Synuclein pathology in PINK1 knockout rat brains. Front. Neurosci. 12:1034. doi: 10.3389/fnn.2018.01034

Creed, R. B., and Goldberg, M. S. (2020). Enhanced susceptibility of PINK1 knockout rats to alpha-synuclein fibrils. Neuroscience 437, 64–75. doi: 10.1016/j.neuroscience.2020.04.032

Creed, R. B., Menalled, L., Casey, B., Dave, K. D., Janssens, H. B., Veinbergs, I., et al. (2019). Basal and evoked neurotransmitter levels in parkin-deficient mice. PLoS One 14:e0238098. doi: 10.1371/journal.pone.0238098

Daher, J. P., Pletnikova, O., Biskup, S., Musso, A., Gellhaar, S., Galter, D., et al. (2012). Neurodegenerative phenotypes in an A53T alpha-synuclein transgenic mouse model are independent of LRRK2. Hum. Mol. Genet. 21, 2420–2431. doi: 10.1093/hmg/dds057

Daves, K. D., De Silva, S., Sheth, N. P., Rambo, S., Beck, M. J., Quang, C., et al. (2014). Phenotypic characterization of recessive gene knockout rat models of Parkinson's disease. Neurobiol. Dis. 70, 190–203. doi: 10.1016/j.nbd.2014.06.009
de Tezanos Pinto, F., and Adamo, H. P. (2018). The strategic function of the PS-ATPase ATP1A2 in toxic waste disposal. Neurochem. Int. 112, 108–113. doi: 10.1016/j.neuint.2017.11.008

Dhunget, N., Eleuteri, S., Li, L. B., Kramer, N. J., Chartron, J. W., Spencer, B., et al. (2015). Parkinson's disease genes DPF35 and EIF4G1 interact genetically and converge on alpha-synuclein. Neuron 85, 76–87. doi: 10.1016/j.neuron.2014.11.027

Di Maio, R., Barrett, P. J., Hoffman, E. K., Barrett, C. W., Zharikov, A., Borah, A., et al. (2016). alpha-Synuclein binds to TOM20 and inhibits mitochondrial protein import in Parkinson's disease. Sci. Transl. Med. 8:342ra378.

Di Notti, M., Masciullo, M., Verrigini, D., Petrillo, S., Modoni, A., Rizzo, V., et al. (2017). DJ-1 modulates mitochondrial response to oxidative stress: clues from a novel diagnosis of PARK7. Clin. Genet. 92, 18–25. doi: 10.1111/cge.12841

Estrada-Cuzcano, A., Martin, S., Chamova, T., Synofzik, M., Timmann, D., Holemans, T., et al. (2017). Loss-of-function mutations in the ATP1A2/PARK9 gene cause complicated hereditary spastic paraplegia (SPG78). Brain 140, 287–305. doi: 10.1093/brain/aww307

Fares, M. B., Jagnnath, S., and Lashuel, H. A. (2021). Reverse engineering Lewy bodies: how far have we come and how far can we go? Nat. Rev. Neurosci. 22, 111–131. doi: 10.1038/s41583-020-00416-6

Farrer, M., Chan, P., Chen, R., Tan, L., Lincoln, S., Hernandez, D., et al. (2001). Lewy bodies and parkinsonism in families with parkin mutations. Ann. Neurol. 50, 293–300.

Fenton, A. R., Jongens, T. A., and Holzbaur, E. L. F. (2021). Mitochondrial dynamics: shaping and remodeling an organelle network. Curr. Opin. Cell Biol. 68, 28–36. doi: 10.1016/j.cob.2020.08.014

Ferre, R., Scala, S., Biagiotti, F., Giardina, E., Zampatti, S., Modugno, N., et al. (2018). Heterozygous PLA2G6 mutation leads to iron accumulation within Basal Ganglia and Parkinson's disease. Front. Neurosci. 9:536. doi: 10.3389/fnene.2018.00536

Funayama, M., Ohe, K., Amo, T., Furuya, N., Yamaguchi, J., Saiki, S., et al. (2015). CHCHD2 mutations in autosomal dominant late-onset Parkinson's disease: a genome-wide linkage and sequencing study. Lancet Neurol. 14, 274–282. doi: 10.1016/S1474-4422(14)70266-2

Ganguly, U., Chakraborti, S. S., Kaur, U., Mukherjee, A., and Chakraborti, S. (2018). Alpha-synuclein, proteotoxicity and Parkinson's disease: search for neuroprotective strategies. Curr. Neuropharmacol. 16, 1086–1097. doi: 10.2174/1570159X15666617129100994

Ganjam, G. K., Bolte, K., Matschke, L. A., Neitemeier, S., Dolga, A. M., Hollerhage, M., et al. (2019). Mitochondrial damage by alpha-synuclein causes cell death in human dopaminergic neurons. Cell Death Dis. 10:865.

Gautier, C. A., Kitada, T., and Shen, J. (2008). Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc. Natl. Acad. Sci. U.S.A. 105, 11364–11369. doi: 10.1073/pnas.0802761105

Goldberg, M. S., Pisani, A., Haburcak, M., Vortherms, T. A., Kitada, T., Costa, M., et al. (2016). alpha-Synuclein binds to TOM20 and inhibits mitochondrial function in toxic waste disposal. Mol. Neurodegener. 11:1399. doi: 10.1186/s12883-016-0137-1

Gupton, J. M., Sheth, N. P., Witting-Stafshede, P., and Hook, F. (2020). Single-vesicle imaging reveals lipid-selective and stepwise membrane disruption by monomeric alpha-synuclein. Proc. Natl. Acad. Sci. U.S.A. 117, 14178–14186.

Harjuhaahto, S., Rasila, T. S., Molchanova, S. M., Woldegebriel, R., Kvist, J., Konovalova, S., et al. (2020). ALS and Parkinson's disease genes CHCHD10
and CHCHD2 modify synaptic transcriptomes in human iPSC-derived motor neurons. *Neurobiol. Dis.* 141:104940. doi: 10.1016/j.nbd.2020.104940

Hierro, A., Rojas, A. L., Rojas, R., Murthy, N., Effantin, G., Kajava, A. V., et al. (2007). Functional architecture of the retromer cargo-recognition complex. *Nature* 449, 1063–1067. doi: 10.1038/nature06216

Hsieh, C. H., Shaltouki, A., Gonzalez, A. E., Bettencourt Da Cruz, A., Burbulla, L. F., St Lawrence, E., et al. (2016). Functional impairment in miro degradation and mitophagy is a shared feature in familial and sporadic Parkinson’s disease. *Cell Stem Cell* 19, 709–724. doi: 10.1016/j.stem.2016.08.002

Ibanez, P., Bonnet, A. M., Debarges, B., Lohmann, E., Tison, F., Pollak, P., et al. (2004). Causal relation between alpha-synuclein gene duplication and familial Parkinson’s disease. *Lancet* 364, 1169–1171. doi: 10.1016/s0140-6736(04)61710-3

Ikeda, A., Nishioka, K., Meng, H., Yamashita, C., Inoshita, T., et al. (2006). Mutations in CHCHD2 cause alpha-synuclein aggregation. *Hum. Mol. Genet.* 28, 3895–3911.

Jiang, Y., Yu, M., Chen, J., Zhou, H., Sun, W., Sun, Y., et al. (2020). Mitochondrial crista structure and destabilizes cytochrome c. *Hum. Mol. Genet.* 60, 588–596.

Kumar, D., Weiselbach, A., Heldmann, M., Kasten, M., Tunc, S., Sue, C. M., et al. (2012). Frequency of the D620N mutation in VPS35 in Parkinson disease. *Am. J. Hum. Genet.* 91, 1144–1148. doi: 10.1016/j.ajhg.2012.09.005

Kumar, N., Leonzino, M., Hancock-Cerutti, W., Horenkamp, F. A., Li, P., Lees, J. A., et al. (2018). VPS13A and VPS13C are lipid transport proteins differentially localized at ER contact sites. *J. Cell Biol.* 217, 3625–3639. doi: 10.1083/jcb.201807019

Leage, S., Drouet, V., Majounie, E., Deramecourt, V., Jacoupy, M., Nicolas, A., et al. (2016). Loss of VPS13C function in autosomal-recessive parkinsonism causes mitochondrial dysfunction and increases PINK1/Parkin-dependent mitophagy. *Am. J. Hum. Genet.* 98, 500–513.

Lin, G., Lee, P. T., Chen, K., Mao, D., Tan, K. L., Zuo, Z., et al. (2018). Phospholipase PLAX2G6, a Parkinsonism-associated gene, affects Vps26 and Vps35, retromer function, and ceramide levels, similar to alpha-synuclein gain. *Cell Metab.* 28, 605–618.e606.

Liu, Y., Clegg, H. V., Leslie, P. L., Du, J., Tolliini, L. A., He, Y., et al. (2015). CHCHD2 inhibits apoptosis by interacting with Bcl-xL to regulate Bax activation. *Cell Death Differ.* 22, 1035–1046. doi: 10.1038/cdd.2014.194

Marchand, A., Drouyer, M., Sarchione, A., Chartier-Harlin, M. C., and Taymans, J. M. (2020). LRRK2 phosphorylation, more than an epiphenomenon. *Front. Neurosci.* 14:527. doi: 10.3389/fnins.2020.00527

Marras, C., Lang, A., Van De Warrenburg, B. P., Sue, C. M., Tabrizi, S. J., Bertram, L., et al. (2017). Nomenclature of genetic movement disorders: recommendations of the International Parkinson and Movement Disorder Society task force. *Mov. Disord.* 32, 724–725. doi: 10.1002/mds.27045

Matsuda, S., Kitagishi, Y., and Kobayashi, M. (2013). Function and characteristics of PINK1 in mitochondria. *Oxid. Med. Cell. Longev.* 2013:601587.

Matsumine, H., Saito, M., Shimoda-Matsubayashi, S., Tanaka, H., Ishikawa, T., Nakagawa-Hattori, Y., et al. (1997). Localization of a gene for an autosomal recessive form of juvenile Parkinsonism to chromosome 6q25.2-27. *Am. J. Hum. Genet.* 60, 588–596.

McWilliams, T. G., Prescott, A. R., Montova-Garriga, L., Ball, G., Singh, F., Barini, E., et al. (2018). Basal mitophagy occurs independently of PINK1 in mouse tissues of high metabolic demand. *Cell Metab.* 27, 439–449.e435.

Meng, H., Yamashita, C., Shiba-Fukushima, K., Inoshita, T., Funayama, M., Sato, S., et al. (2017). Loss of Parkinson’s disease-associated protein CHCHD2 affects mitochondrial cristae structure and destabilizes cytochrome c. *Nat. Commun.* 8:15500.

Miller, D. W., Hague, S. M., Clarimon, J., Baptista, M., Gwinn-Hardy, K., Cookson, M. R., et al. (2004). Alpha-synuclein in blood and brain from familial Parkinson disease with SNCA locus triplication. *Neurology* 62, 1835–1838. doi: 10.1212/01.wnl.0000127517.33208.f4

Mir, R., Tonelli, F., Lis, P., Macartney, T., Polinski, N. K., Martinez, T. N., et al. (2018). The Parkinson’s disease VPS35[D620N] mutation enhances LRRK2-mediated Rab protein phosphorylation in mouse and human. *Biochem. J.* 475, 1861–1883. doi: 10.1042/bj20180248

Miura, E., Hasegawa, T., Konno, M., Suzuki, M., Sugeno, N., Fujiakake, N., et al. (2014). VPS13C dysfunction impairs lysosomal degradation of alpha-synuclein and exacerbates neurotoxicity in a Drosophila model of Parkinson’s disease. *Neurobiol. Dis.* 71, 1–13. doi: 10.1016/j.nbd.2014.07.014

Miyakawa, S., Ogino, M., Funabe, S., Uchino, A., Shimo, Y., Hattori, N., et al. (2013). Lewy body pathology in a patient with a homozygous parkin deletion. *Mov. Disord.* 28, 388–391.

Modjtabahi, N., Tokatli, K., Dessen, P., and Kroemer, G. (2016). Mitochondrial proteins containing coiled-coil-helix-coiled-helix (CHCH) domains in health and disease. *Trends Biochem. Sci.* 41, 245–260. doi: 10.1016/j.tibs.2015.12.004

Morgan, N. V., Westaway, S. K., Morton, J. E., Gregory, A., Gissen, P., Sunek, S., et al. (2006). PLA2G6 encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat. Genet.* 38, 752–754. doi: 10.1038/ng1826

Mori, A., Hatano, T., Inoshita, T., Shiba-Fukushima, K., Koinuma, T., Meng, H., et al. (2019). Parkinson’s disease-associated iPLA2-ALVA/iPLA2G6 regulates neuronal functions and alpha-synuclein stability through membrane remodeling. *Proc. Natl. Acad. Sci. U.S.A.* 116, 20689–20699. doi: 10.1073/pnas.1902884116

Nybo, C. J., Gustavsson, E. K., Farrer, M. J., and Aasly, J. O. (2020). Neuropathological findings in PINK1-associated Parkinson’s disease. *Parkinsonism Relat. Disord.* 78, 105–108. doi: 10.1016/j.parkreldis.2020.07.023
Onishi, M., Yamano, K., Sato, M., Matsuda, N., and Okamoto, K. (2021). Molecular mechanisms and physiological functions of mitophagy. EMBO J. 40: e104705.

Ozawa, K., Tsumoto, H., Miura, Y., Yamaguchi, J., Iguchi-Ariga, S. M. M., Sakuma, T., et al. (2020). DJ-1 is dispensable for the S-nitrosylation of Parkin, which maintains function of mitophagosomes. Sci. Rep. 10:4377.

Paisan-Ruiz, C., JAIN, S., EVANS, E. W., GILKS, W. P., SIMON, J., VAN DER BRUG, M., et al. (2004). Cloning of the gene containing mutations that cause PARK8-linked Parkinson’s disease. Neuron 44, 595–600. doi: 10.1016/j.neuron.2004.10.023

Paisan-Ruiz, C., LI, A., SCHNEIDER, S. A., HOLTON, J. L., JOHNSON, R., KIDD, D., et al. (2012). Widespread Lewy body and tau accumulation in childhood and adult onset dystonia-parkinsonism cases with PLA2G6 mutations. Neurobiol. Aging 33, 814–823. doi: 10.1016/j.neurobiaging.2010.05.009

Pang, S. Y., HO, P. W., LIU, H. F., LEUNG, C. T., LI, L., CHANG, E. E. S., et al. (2019). The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson’s disease. Transl. Neurodegener. 8:23.

Park, J. H., BURGESS, J. D., FAROQUI, A. H., DOMEYKO, S. M., SAUNDERS, P., et al. (2017). DJ-1 is a redox sensitive adapter protein for high molecular weight complexes involved in regulation of catecholamine homeostasis. Mol. Neurodegener. 15:5.

Park, J., KOENTJORO, B., VEIVERIS, D., MACKAY-SIM, A., and SUE, C. M. (2014). DJ-1 and PINK1 co-operate to control mitochondrial function and autophagy. J. Cell Sci. 127, 176–182. doi: 10.1242/jcs.190715

Podhajska, A., Musso, A., TRANCIKOVA, A., STAFA, K., MØSER, R., SONNAY, S., et al. (2016). PARK5 harbors mutations in PINK1 leading to autosomal-recessive Parkinson’s disease. Hum. Mol. Genet. 25, 4028–4041. doi: 10.1093/hmg/ddx294

Podhajska, A., MUSSO, A., TRANCIKOVA, A., STAF, K., MØSER, R., SONNAY, S., et al. (2012). Common pathogenic effects of missense mutations in the P-type ATPase ATP13A2 (PARK9) deficiency cause Parkinson’s disease. Hum. Mol. Genet. 21, 2299–2310. doi: 10.1093/hmg/ddq324

Ramsey, C. P., and GIASSON, B. I. (2010). L10p and P158DEL DJ-1 mutations cause dominantly-negative mechanism. Brain 133, 978–981. doi: 10.1093/brain/awq178

Rasmussen, B., KEMLINK, D., MOLENHAUER, B., FIALA, O., MACHETANZ, G., ROTH, J., et al. (2018). Diagnostic exome sequencing in early-onset Parkinson’s disease confirms VPS13C as a rare cause of autosomal-recessive Parkinson’s disease. Clin. Genet. 93, 603–612. doi: 10.1111/cge.13124

Schulte, C., and GASSER, T. (2011). Genetic basis of Parkinson’s disease: inheritance, penetrance, and expression. Appl. Clin. Genet. 4, 67–80. doi: 10.2147/accg.s11639

Shahmoradian, S. H., LEWIS, A. J., GENOU, C., HENCH, J., MOORES, T. E., NAVARRO, P. P., et al. (2019). Lewy pathology in Parkinson’s disease consists of crowded organelles and lipid membranes. Nat. Neurosci. 22, 1099–1109. doi: 10.1038/s41593-019-0423-2

Shendelmann, S., JONASON, A., MARTINAT, C., LEEF, T., and ABELIOVICH, A. (2004). DJ-1 is a redox-dependent molecular chaperone that inhibits alpha-synuclein aggregate formation. PLoS Biol. 2:e362. doi: 10.1371/journal.pbio.0020362

Shimura, H., SCHLOSSMACHER, M. G., HATTORI, N., FROSH, M. P., TROCKENBACHER, A., SCHNEIDER, R., et al. (2001). Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson’s disease. Science 293, 263–269. doi: 10.1126/science.1060627

Shojaaee, S., SIN, F., BANISHOESSEINI, S. S., KAZEMI, M. H., KHALR, R., SHAHIDI, G. A., et al. (2008). Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. Am. J. Hum. Genet. 82, 1373–1384. doi: 10.1016/j.ajhg.2008.05.005

Sta˚da, J., JASINSKA-MyGA, B., BOCZARSKA-JEDYNAK, M., OPAŁA, G., FIESEL, F. C., MOUSAUD-LAMODIERE, E. L., et al. (2014). Early-onset Parkinson’s disease due to PARK1 p.Q456X mutation—clinical and functional study. Parkinsonism Relat. Disord. 20, 1274–1278. doi: 10.1016/j.parkreld.2014.08.019

Slitter, D. A., MARTINEZ, J., HAO, L., CHEN, X., SUN, N., FISCHER, T. D., et al. (2018). Parkin and PARK1 mitigate STING-induced inflammation. Nature 561, 258–262. doi: 10.1038/s41586-018-0448-9

Smolders, S., PHIJLJENS, S., CROSiers, D., SIEBEN, A., HENS, E., HEEMAN, B., et al. (2021). Contribution of rare homozygous and compound heterozygous VPS13C missense mutations to dementia with Lewy bodies and Parkinson’s disease. Acta Neuropathol. Commun. 9:25.

Spataro, R., KOUISI, M., FARHAN, S. M. K., WILLER, J. R., ROSS, J. P., DIoN, P. A., et al. (2019). Mutations in ATP13A2 (PARK9) are associated with an amyotrophic lateral sclerosis-like phenotype, implicating this locus in further phenotypic expansion. Hum. Genomics 13:19.

Suni-Akamaru, H., BECK, G., SHINZAWA, K., KATO, S., RIKI, Y., YOSHIDA, M., et al. (2016). High expression of alpha-synuclein in damaged mitochondria with PLA2G6 dysfunction. Acta Neuropathol. Commun. 4:27.

Surmeier, D. J., OBESO, J. A., and HALLIDAY, G. M. (2017). Parkinson’s disease is not simply a prion disorder. J. Neurosci. 37, 9979–9980. doi: 10.1523/jneurosci.1787-16.2017

Tabuchi, M., Yanatori, I., Kawai, Y., and KISHI, F. (2010). Retromer-mediated direct sorting is required for proper endosomal recycling of the mammalian iron transporter DMT1. J. Cell Sci. 123, 756–766. doi: 10.1242/jcs.060574

Taipa, R., Pereira, C., REIS, I., ALONSO, I., BASTOS-LIMA, A., MELo-Pires, M., et al. (2016). DJ-1 linked parkinsonism (PARK7) is associated with Lewy body pathology. Brain 139, 1680–1687. doi: 10.1093/brain/aww080

Takahashi, M., LI, Y., and HATTORI, N. (2016). Absence of Lewy pathology associated with PARK1 homozygous mutation. Neurology 86, 2212–2213. doi: 10.1212/wnl.000000000002744

Tan, M. X., Malek, N., LAWTON, M. A., HUBBARD, L., PITMAN, A. M., Joseph, T., et al. (2019). Genetic analysis of Mendelian mutations in a large UK population-based Parkinson’s disease study. Brain 142, 2828–2844. doi: 10.1093/brain/awv191

Tang, F. L., LIU, W., HU, J. X., ERION, J. R., YE, J., MEI, L., et al. (2015). VPS55 deficiency or mutation causes dopaminergic neuronal loss by impairing mitochondrial fusion and function. Cell Rep. 12, 1631–1643. doi: 10.1016/j.celrep.2015.08.001

Thomas, K. J., MCCOY, M. K., Blackinton, J., BELINA, A., VAN DER BRUG, M., Sandebring, A., et al. (2011). DJ-1 acts in parallel to the PARK1/parkin pathway to control mitochondrial function and autophagy. Hum. Mol. Genet. 20, 40–50. doi: 10.1093/hmg/ddq191

Tian, Y., TANG, F. L., SUN, W., XEN, W., MEI, L., TANG, B. S., et al. (2015). VPS55 deficiency results in impaired AMPA receptor trafficking and decreased dendritic spine maturation. Mol. Brain 8:70.
Tran, J., Anastacio, H., and Bardy, C. (2020). Genetic predispositions of Parkinson’s disease revealed in patient-derived brain cells. *NDJ Parkinsons Dis.* 6:8.
Trempe, J. F., and Fon, E. A. (2013). Structure and function of parkin, PARK1, and DJ-1, the three musketeers of neuroprotection. *Front. Neurol.* 4:38. doi: 10.3389/fneur.2013.00021
Trempe, J. F., Sauve, V., Grenier, K., Seirafi, M., Tang, M. Y., Menade, M., et al. (2013). Structure of parkin reveals mechanisms for ubiquitin ligase activation. *Science* 340, 1451–1455. doi: 10.1126/science.1237908
Tsunemi, T., and Kainc, D. (2014). Zn(2+)(+) dyshomeostasis caused by loss of ATP13A2/PARK9 leads to lysosomal dysfunction and alpha-synuclein accumulation. *Hum. Mol. Genet.* 23, 2791–2801. doi: 10.1093/hmg/ddt572
Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., et al. (2004). Hereditary early-onset Parkinson’s disease caused by mutations in PARK1. *Science* 304, 1158–1160. doi: 10.1126/science.1096284
van Veen, S., Martin, S., Van Den Haute, C., Benoy, V., Lyons, J., Vanhoutte, R., et al. (2020). ATP13A2 deficiency disrupts lysosomal polyamine export. *Nature* 578, 419–424. doi: 10.1038/s41586-020-1968-7
Wang, H., Ni, H. M., Chao, X., Ma, X., Rodriguez, Y. A., Chavan, H., et al. (2019). Double deletion of PARK1 and Parkin impairs hepatic mitophagy and exacerbates acetaminophen-induced liver injury in mice. *Redox Biol.* 22:101148. doi: 10.1016/j.redox.2019.101148
Wang, W., Ma, X., Zhou, L., Liu, J., and Zhu, X. (2017). A conserved retromer sorting motif is essential for mitochondrial DLP1 recycling by VPS35 in Parkinson’s disease model. *Hum. Mol. Genet.* 26, 781–789.
Wang, W., Wang, X., Fujioka, H., Hoppel, C., Whone, A. L., Caldwell, M. A., et al. (2016). Parkinson’s disease-associated mutant VPS35 causes mitochondrial dysfunction by recycling DLP1 complexes. *Nat. Med.* 22, 54–63. doi: 10.1038/nm.3983
Wauters, F., Cornelissen, T., Imberechts, D., Martin, S., Koentjoro, B., Sue, C., et al. (2020). LRRK2 mutations impair depolarization-induced mitophagy through inhibition of mitochondrial accumulation of RAB10. *Autophagy* 16, 203–222. doi: 10.1080/15548627.2019.1603548
Weindel, C. G., Bell, S. L., Vail, K. J., West, K. O., Patrick, K. L., and Watson, R. O. (2020). LRRK2 maintains mitochondrial homeostasis and regulates innate immune responses to Mycobacterium tuberculosis. *Elife* 9:e51071.
Whiffin, N., Armean, I. M., Kleinman, A., Marshall, J. L., Minkel, E. V., Goodrich, J. K., et al. (2020). The effect of LRRK2 loss-of-function variants in humans. *Nat. Med.* 26, 869–877.
Wider, C., Skipper, L., Solida, A., Brown, L., Farrer, M., Dickson, D., et al. (2008). Autosomal dominant dopa-responsive parkinsonism in a multigenerational Swiss family. *Parkinsonism Relat. Disord.* 14, 465–470. doi: 10.1016/j.parkreldis.2007.11.013
Williams, E. T., Chen, X., and Moore, D. J. (2017). VPS35, the retromer complex and Parkinson’s disease. *J. Parkinson’s Dis.* 7, 219–233.
Winston, J. T., Koep, D. M., Zhu, C., Eldridge, S. J., and Harper, J. W. (1999). A family of mammalian F-box proteins. *Curr. Biol.* 9, 1180–1182. doi: 10.1016/S0960-9822(99)80021-4
Xiong, Y., Neifert, S., Karuppagounder, S. S., Stankowski, J. N., Lee, B. D., Grima, J. C., et al. (2017). Overexpression of Parkinson’s disease-associated mutation LRRK2 G2019S in mouse forebrain induces behavioral deficits and alpha-synuclein pathology. *eNeuro* 4:e0004.
Xu, C. Y., Kang, W. Y., Chen, Y. M., Jiang, T. F., Zhang, J., Zhang, L. N., et al. (2017). DJ-1 inhibits alpha-synuclein aggregation by regulating chaperone-mediated autophagy. *Front. Aging Neurosci.* 9:308. doi: 10.3389/fnagi.2017.00308
Zambon, F., Cherubini, M., Fernandes, H. J. R., Lang, C., Ryan, B. J., Volpato, V., et al. (2019). Cellular alpha-synuclein pathology is associated with bioenergetic dysfunction in Parkinson’s iPSC-derived dopamine neurons. *Hum. Mol. Genet.* 28, 2001–2013. doi: 10.1093/hmg/ddz038
Zhao, T., Severijnen, L. A., Van Der Weiden, M., Zheng, P. P., Oostra, B. A., Hukema, R. K., et al. (2013). FBXO7 immunoreactivity in alpha-synuclein-containing inclusions in Parkinson disease and multiple system atrophy. *J. Neuropathol. Exp. Neurol.* 72, 482–488. doi: 10.1097/nen.0b013e318293c586
Zhou, Z. D., Sathiyamoorthy, S., Angeles, D. C., and Tan, E. K. (2016). Linking F-box protein 7 and parkin to neuronal degeneration in Parkinson’s disease (PD). *Mol. Brain* 9:41.
Zhou, Z. D., Xie, S. P., Sathiyamoorthy, S., Saw, W. T., Sing, T. Y., Ng, S. H., et al. (2015). F-box protein 7 mutations promote protein aggregation in mitochondria and inhibit mitophagy. *Hum. Mol. Genet.* 24, 6314–6330. doi: 10.1093/hmg/ddv340
Zondler, L., Miller-Fleming, L., Repici, M., Goncalves, S., Tenreiro, S., Rosado-Ramos, R., et al. (2014). DJ-1 interactions with alpha-synuclein attenuate aggregation and cellular toxicity in models of Parkinson’s disease. *Cell Death Dis.* 5:e1350. doi: 10.1038/cddis.2014.307

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Copyright © 2021 Li, Fu, Halliday and Sue. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.**