Parkinson Disease from Mendelian Forms to Genetic Susceptibility: New Molecular Insights into the Neurodegeneration Process

Amin Karimi-Moghadam1 · Saeid Charsouei2 · Benjamin Bell3 · Mohammad Reza Jabalameli1,3

Received: 12 February 2018 / Accepted: 20 April 2018 / Published online: 26 April 2018
© The Author(s) 2018

Abstract
Parkinson disease (PD) is known as a common progressive neurodegenerative disease which is clinically diagnosed by the manifestation of numerous motor and nonmotor symptoms. PD is a genetically heterogeneous disorder with both familial and sporadic forms. To date, researches in the field of Parkinsonism have identified 23 genes or loci linked to rare monogenic familial forms of PD with Mendelian inheritance. Biochemical studies revealed that the products of these genes usually play key roles in the proper protein and mitochondrial quality control processes, as well as synaptic transmission and vesicular recycling pathways within neurons. Despite this, large number of patients affected with PD typically tends to show sporadic forms of disease with lack of a clear family history. Recent genome-wide association studies (GWAS) meta-analyses on the large sporadic PD case–control samples from European populations have identified over 12 genetic risk factors. However, the genetic etiology that underlies pathogenesis of PD is also discussed, since it remains unidentified in 40% of all PD-affected cases. Nowadays, with the emergence of new genetic techniques, international PD genomics consortiums and public online resources such as PDGene, there are many hopes that future large-scale genetics projects provide further insights into the genetic etiology of PD and improve diagnostic accuracy and therapeutic clinical trial designs.

Keywords Parkinson disease · Neurodegeneration · Autophagy · Mitochondrial dysfunction · Oxidative stress · GWAS meta-analysis

Introduction
Parkinson’s disease (PD) was first described by James Parkinson, an English doctor, in 1817 (Kempster et al. 2007). PD is known as a chronic, progressive neurodegenerative disease that affects 2% of the population over the age of 60 and 4% of the population over the age of 80 (late-onset PD). However, 10% of the disease can occur in younger adults, between 20 and 50 years of age (early-onset PD). Besides the age, several studies have found evidence of gender influence in the incidence of PD. It has been proven that PD is more prevalent in men than in women, with a ratio of 3:1, respectively; which may be attributable to the effect of estrogen on dopaminergic neurons and pathways in the brain (Schrag et al. 2000). PD is classically diagnosed by the manifestation of impaired motor function with an asymmetric onset that spreads with time to become bilateral. The majority motor impairments of PD arise owing to the dopaminergic neural loss in the substantia nigra pars compacta and the subsequent loss of dopamine input to forebrain (striatal) motor structures, leading to debilitating problems with tremor, muscular rigidity, and bradykinesia (slowness of movement) (Jankovic 2008). However, recent studies have recognized PD as a more complex disorder encompassing both motor (MS) and nonmotor symptoms (NMS). It has been proven that the occurrence of NMS is more prevalent among patients with PD and the frequency of them increases with the disease severity or during the course of the disease. Most patients with the long-term disease or severe pathology show 6–10 NMS. Also, there is increasing evidence that NMS such as sensory abnormalities (olfactory deficits), sleep disturbance (rapid eye movement), depression,
autonomic dysfunction, and cognitive decline may precede the onset of motor signs of Parkinson’s disease (Jankovic 2008; O’Sullivan et al. 2008). Therefore, NMS or premotor symptoms of the disease would be very informative for early diagnosis and identification of apparently normal older individuals with the full constellation of premotor signs and introducing neuroprotective strategies at an early stage in order to develop effective treatments for the disease (Berg et al. 2012; Stern et al. 2012).

Originally, PD has been identified as a genetically heterogeneous disorder which is classified into two genetic subtypes including monogenic familial forms with Mendelian inheritance and sporadic forms with no or less obvious familial aggregation. It has been proven that monogenic familial forms are caused by rare, highly penetrant pathogenic mutations; however, sporadic forms may result from contributions of environmental factors and genetic susceptibility (Davie 2008; De Lau and Breteler 2006; Lesage and Brice 2009; Taccioli et al. 2011). Now, considering the availability of high-throughput genetic analysis techniques and the access to large patient samples such as the International PD Genomics Consortium (IPDGC), the amount of information in the field of PD genetics in both areas is quickly growing. The aim of this review is to provide an overview of the recent genetic findings in both areas of familial and sporadic forms of PD disease.

Familial PD

Researches in the field of Parkinsonism have reported that approximately 10% of all PD-affected cases typically tend to show a clear Mendelian inheritance pattern and familial aggregation associated with the high risk of PD recurrence (Hardy et al. 2009). Over the past decades, through the genetic studies in these families, at least 23 disease-segregating genes or loci causing various monogenic forms of PD have been identified so far (Table 1). The knowledge acquired from the protein products of these genes indicates that mitochondrial dysfunctions and impaired autophagy-based protein or organelle degradation pathways all play key roles in the neurodegeneration process within brain and pathogenesis of PD (Mullin and Schapira 2013; Ryan et al. 2015). Here, the genes implicated in Mendelian forms of PD are reviewed.

SNCA

Synuclein-Alpha (SNCA) was the first PD-associated gene to be identified and is inherited in an autosomal dominant manner (Polymeropoulos et al. 1996). Patients affected with SNCA mutations exhibit clinically late-onset and typical features of PD. However, several mutations have been identified to be associated with early-onset PD phenotypes and more severe features, including rapid progression of bradykinesia, rigidity and tremor, high prevalence of psychiatric symptoms, frequent dementia, prominent cognitive decline, autonomic dysfunctions, and moderate response to levodopa (1,3,4-dihydroxyphenylalanine; l-DOPA), which is a dopamine receptor agonist (Ibáñez et al. 2009; Lesage et al. 2013; Polymeropoulos et al. 1997). SNCA encodes a presynaptic protein (α-synuclein) and plays an important role in synaptic transmission (Liu et al. 2004). Several in vivo gene expression analyses have provided evidence for SNCA positive effects on synaptic vesicle recycling and mobilization in the proximity of axon terminal by its involvement in the regulation of phospholipase D2 activity and induction of lipid droplet accumulation (Lotharius and Brundin 2002). Consistent with these analyses, some related experiments on animal models demonstrated that SNCA is associated with the synaptic plasticity by enhancing neurotransmitter release from the axon terminal (Nemani et al. 2010). In addition, several other studies have indicated the possible negative regulatory effect of SNCA on tyrosine hydroxylase activity, a rate-limiting enzyme in dopamine biosynthesis (Yu et al. 2004).

As illustrated in Table 1, to date, three classes of pathogenic mutations have been identified in SNCA gene: (1) missense point mutations in the coding region of SNCA, (2) dinucleotide repeat variation in the promoter region of SNCA, and (3) locus multiplications, including duplications and triplications, resulted from intra-allelic or inter-allelic unequal crossing over between Alu and LINE elements for segmental duplication, and both mechanisms for SNCA triplication. Quantitative gene expression analyses have proven that two last classes lead to pathogenic overexpression of the wild-type protein (Kojovic et al. 2012; Mutez et al. 2011).

SNCA mutations are suspected to have specific toxic effects in dopaminergic neurons. It seems that mutations in SNCA reduce the affinity of α-synuclein for lipids, thus increasing the tendency of the protein to form oligomers through a concentration-dependent mood, and consequently accelerate the formation of toxic α-synuclein fibrils (the major component of Lewy bodies) (Winner et al. 2011). It has been demonstrated that wild-type α-synuclein physically interacts with lysosome-associated membrane protein 2A (LAMP-2A), a transmembrane receptor for selective translocation of proteins into isolated lysosomes for the chaperone-mediated autophagy (CMA) pathway, providing support for the idea that CMA is involved in α-synuclein clearance (Fig. 1a). In fact, some pathogenic mutations in α-synuclein increase their affinity for LAMP-2A and act as uptake blockers, inhibiting both their own autophagy-dependent clearance and that of other CMA substrates. These studies provide another potential clue to the correlation of toxic
gain of function mutations in α-synuclein with the lesions in PD (Cuervo et al. 2004; Wang and Mao 2014; Xilouri et al. 2016). Also, there is a hypothesis that a deficit in neurotransmitter release due to α-synuclein mutation could lead to cytoplasmic accumulation of dopamine, and increase oxidative stress and metabolic dysfunction in dopaminergic

| Loci   | Inheritance | Gene     | Position | Protein                          | Disease onset             | Mutations                                           |
|--------|-------------|----------|----------|----------------------------------|---------------------------|----------------------------------------------------|
| PARK1  | AD rare sporadic | SNCA     | 4q21     | Synuclein-alpha                  | Early onset rarely late onset | Missense; regulatory gene duplication or triplication |
| PARK2  | AR sporadic | PARKIN   | 6q25–q27 | E3 ubiquitin ligase              | Early onset               | Missense or nonsense; regulatory; splicing; small indels; deletions; insertions |
| PARK3  | AD          | Unknown  | 2p13     | Unknown                          | Late onset                | Unknown                                            |
| PARK4  | AD rare sporadic | SNCA     | 4q21     | Synuclein-alpha                  | Early onset rarely late onset | Missense; regulatory gene duplication or triplication |
| PARK5  | AD          | UCHL1    | 4p14     | Ubiquitin C-terminal hydrolase L1 | Late onset                | Missense                                           |
| PARK6  | AR          | PINK1    | 1p35–p36 | PTEN-induced kinase              | Early onset               | Missense or nonsense; splicing; small indels; deletions; insertions |
| PARK7  | AR          | DJ-1     | 1p36     | DJ-1                             | Early onset               | Missense; regulatory; splicing; small indels; deletions; insertions |
| PARK8  | AD sporadic | LRRK2    | 12q12    | Leucine-rich repeat kinase 2     | Late onset                | Missense; splicing; small deletions                |
| PARK9  | AR          | ATP13A2  | 1p36     | Cation-transporting ATPase 13A2  | Early onset               | Missense; splicing; small indels; deletions; insertions |
| PARK10 | Unclear     | Unknown  | 1p32     | Unknown                          | Unclear                   | Unknown                                            |
| PARK11 | AD          | GIGYF2   | 2q36–q37 | GRB10 interacting GYF protein 2  | Late onset                | Missense; small indels                             |
| PARK12 | Unclear     | Unknown  | Xq21–q25 | Unknown                          | Unclear                   | Unknown                                            |
| PARK13 | AD          | Omi/HTRA2| 2p13     | Serine peptidase 2               | Late onset                | Missense; splicing                                 |
| PARK14 | AR          | PLA2G6   | 22q12–q13| Phospholipase A2, group 6        | Early onset               | Missense; splicing; deletions; insertions          |
| PARK15 | AR          | FBXO7    | 22q12–q13| F-box protein 7                  | Early onset               | Missense; splicing                                 |
| PARK16 | AD          | VPS35    | 16q11.2  | Vacuolar protein sorting 35      | Late onset                | Missense; splicing                                 |
| PARK17 | AD          | EIF4G1   | 3q27.1   | Eukaryotic translation initiation factor 4 gamma, 1 | Late onset | Missense; deletions; insertions |
| PARK18 | AD          | DNAJC6   | 1p31.3   | DNAJ subfamily C member 6        | Early onset               | Missense or nonsense; splicing                     |
| PARK19 | AR          | SYNJ1    | 21q22.1  | Synaptotagmin-1                  | Early onset               | Missense                                           |
| PARK20 | AR          | DNAJC13  | 3q22.1   | DNAJ subfamily C member 13       | Early onset               | Missense                                           |
| PARK21 | AD          | CHCHD2   | 7p11.2   | Coiled-coil-helix-coiled-helix domain 2 | Late onset | Missense                                           |
| PARK22 | AD          | VPS13C   | 15q22.2  | Vacuolar protein sorting 13C     | Early onset               | Missense; small deletion                           |
| −      | AD for PD   | GBA      | 1q21     | Glucocerebrosidase               | Unclear                   | Missense; regulatory; splicing; small indels; deletions; insertions (CAG) three nucleotide repeat variations |
| −      | AR for GD   | SCA2     | 12q24.1  | Spinocerebellar ataxia type 2    | Unclear                   | Missense                                           |
neurons (Lotharius and Brundin 2002), resulting from increased nonenzymatic and enzymatic oxidation of dopamine (Stefanis 2012). This finding has been corroborated by the Petrucelli et al. (2002) observations that mutant α-synuclein was selectively toxic to tyrosine hydroxylase positive neuroblastoma cells, but not in the neurons lacking tyrosine hydroxylase (Petrucelli et al. 2002).

PARKIN

The second type of PD is caused by mutations in the PAR-KIN gene which leads to the autosomal recessive juvenile Parkinsonism (ARJP), the most prevalent known cause of early-onset (before age 45 years) PD (49% of familial early-onset PD and 15% of sporadic early-onset PD). Lücking et al. (2000) elucidated that there is a significant decline in the frequency of PARKIN mutations with increasing age at PD onset (Lücking et al. 2000). In particular, PD onset occurs before the age of 20, in 80% of patients with homozygous or compound heterozygous mutations in PARKIN gene (Klein et al. 2003; Mata et al. 2004; Periquet et al. 2003). It is now evident that mutations in PARKIN are associated with early development of motor symptoms, hyperreflexia, bradykinesia, dystonia, tremor, good response to low dose of l-DOPA at onset, and later l-DOPA-induced dyskinesia, as well as slow progression of psychiatric symptoms, with any clinical evidence of dementia (Ishikawa and Tsuji 1996; Ebba; Lohmann et al. 2003, 2009). Functionally, PARKIN is considered as a member of a multiprotein E3 ubiquitin ligase complex required for covalent attachment of activated ubiquitin molecules to target substrates (Shimura et al. 2000). This process is performed by a reaction cascade consisting of three groups of enzymes, including E1 ubiquitin-activating enzyme (UbA1), E2 ubiquitin-conjugating enzymes (UbCH7), and PARKIN E3 ubiquitin ligase (Pao et al. 2016; Trempe et al. 2013). The PARKIN-mediated ubiquitylation has various functional consequences, including the proteasomal degradation of misfolded or damaged proteins (Tanaka et al. 2004). It now appears that PARKIN also controls the mitochondrial quality through the selective lysosome-dependent degradation (autophagy or mitophagy) of dysfunctional mitochondria (Ryan et al. 2015).

As illustrated in Table 1, different types of mutations have been identified within PARKIN gene. Interestingly, it has proven that most of PARKIN mutation carriers have exon rearrangements in the heterozygous state (Stenson et al. 2017).

Mutations in PARKIN gene are associated with significant degeneration of dopaminergic neurons in the substantia nigra (Hristova et al. 2009). The presence of protein inclusions in Lewy bodies in PD patients led to the hypothesis that mutations in PARKIN cause a disruption in the E3

---

**Fig. 1** Lysosome-dependent degradation pathways; As indicated, a toxic α-synuclein aggregates are selectively degraded within the lysosome by means of LAMP-2A and chaperones; b GBA catalyzes the breakdown of sphingolipid glucosyleramide to ceramide and glucose within the lysosome; c damaged mitochondria is preferentially degraded by autophagosomal membrane engulfment and subsequent fusion with lysosome; d ATP13A2 is located inside the lysosomal membrane and its proper function is essential to the lysosomal membrane stability.
ubiquitin ligase activity of PARKIN, leading to insufficient clearance of damaged or mutated substrates and subsequent toxic cellular aggregation of unwanted proteins and neuronal cell death (Shimura et al. 2000). In addition, there is an idea that mutations in the PARKIN gene affect another important role of PARKIN in the turnover of mitochondria, reducing the ability of cells to remove damaged mitochondria by autophagy or mitophagy pathway (Pickrell and Youle 2015).

**PINK1**

Homozygous or compound heterozygous mutations in PTEN-induced kinase (PINK1) gene are considered as the second leading cause of recessive early-onset PD (Valente et al. 2004). Clinically, patients with mutations in PINK1 tend to present symptoms before the age of 40 and longer mean disease durations (Ibáñez et al. 2006). It has been described that the frequency of mutations varies between different populations from 1 to 15% (Nuytemans et al. 2010). Also, it has been proven that the clinical phenotype of PD appears to be broadly similar between patients with PARKIN and PINK1 mutations, suggesting the idea that they might act together in pathways relevant to PD pathogenesis (Ibáñez et al. 2006). Interestingly, studies in Drosophila and mice also indicated a common PINK1/PARKIN pathway important for maintaining mitochondrial fidelity (Burman et al. 2012; Damiano et al. 2014; Moisoi et al. 2014; Park et al. 2006). Moreover, there are some indications that PINK1 gene encodes a mitochondrial serine/threonine protein kinase and plays several important roles in mitochondrial pathways, including mitophagy, mitochondrial trafficking, and mitochondrial dynamics (Itoh et al. 2013; Narendra et al. 2010; Xinnan; Wang et al. 2011), which are largely consistent with the previous notion of PINK1/PARKIN common function in mitochondrial pathways.

Some mutations in PINK1 may decrease the stability of the protein, whereas others significantly reduce the phosphorylation or kinase activity, supporting the hypothesis that mitochondrial dysfunction and oxidative stress may be associated with the PD (Deas et al. 2009; Gautier et al. 2008).

**PINK1, PARKIN, and Mitochondrial Hemostasis**

Selective autophagic degradation of damaged mitochondria is necessary for mitochondrial homeostasis, an essential process for the cell survival (Franco-Iborra et al. 2016; McLellan et al. 2014). Cell biology studies revealed that PARKIN is selectively activated and recruited to depolarized mitochondria in order to drive damaged mitochondrial degradation (Vives-Bauza et al. 2010). PINK1 detects bioenergetically defective mitochondria, accumulates on it, and subsequently recruits PARKIN from the cytosol and instigates its E3 ubiquitin ligase activity by its kinase activity to trigger a cellular process for a selective degradation of mitochondria by autophagy (Kondapalli et al. 2012).

PINK1 functions as a kind of molecular sensor, monitoring the internal state of individual mitochondria and flagging damaged mitochondria for removal (Matsuda et al. 2010). With respect to PINK1 roles in mitophagy, the damage-sensing mechanisms arise from the localization-dependent degradation of PINK1 in healthy mitochondria within a cell, which regulates PINK1 cytoplasmic concentration (Thomas et al. 2014). Under normal steady-state conditions, PINK1 is imported into the outer mitochondrial membrane (OMM) and thereby inner mitochondrial membrane (IMM), respectively, through the translocase of the outer membrane (TOM) and translocase of the inner membrane (TIM) complexes, cleaved by the IMM protease called Presenilin-associated rhomboid-like protein (PARL) and another mitochondrial processing peptidase (MPP), and subsequently degraded by the ubiquitin–proteasome system. This mechanism causes an undetectable concentration of PINK1 molecules on healthy mitochondria (Greene et al. 2012; Jin et al. 2010; Meissner et al. 2011). See Fig. 2a.

It has appeared that electrical component of the inner mitochondrial membrane potential (ΔΨ) is crucial for the direction of PINK1 towards mitochondrial membrane and for its import into mitochondrial matrix compartment. The collapse of ΔΨ blocks the TOM/TIM import pathway and in turn, prevents PARL/MPP rapid degradation mechanism causing PINK1 to accumulate uncleaved on the OMM, and binds to the outer mitochondrial membrane proteins such as TOM complex. When PINK1 becomes stable on the OMM, recruits PARKIN and activates its E3 ubiquitin ligase activity to enable OMM proteins polyubiquitination (Lazarou et al. 2012; Okatsu et al. 2013; Youle and Narendra 2011). Figure 2b shows that PINK1-mediated recruitment and activation of PARKIN occurs through Ser65 phosphorylation within the ubiquitin-like (Ubl) domain of PARKIN (Kazlauskaite et al. 2014). However, several recent biochemical investigations found that this process can be accelerated when PARKIN Ser65 phosphorylation combined with ubiquitin Ser65 phosphorylation (Kane et al. 2014). A model is presented for this positive feedback showing that phospho-ubiquitin generated by PINK1 (not modified ubiquitin) likely functions as an allosteric effector, binds to PARKIN allosteric site, and regulates its E3 ubiquitin ligase activity in a positive manner (Koyano et al. 2014).

Once PARKIN is activated, it modifies various proteins on the OMM (36 substrates have been identified to date) and in the cytosol with K48- and K63-linked ubiquitin chains and thereby facilitates recruitment of specific autophagic receptor to ultimately degrade damaged mitochondria (Chan et al. 2011; Sarraf et al. 2013).
It has been reported that PINK1/PARKIN pathway facilitates mitophagy by altering mitochondrial trafficking (Xinnan Wang et al. 2011). Miro1 is a mitochondrial outer membrane protein that forms a complex with Milton and Kinesin to promote mitochondrial trafficking on microtubules (Boldogh and Pon 2007; Frederick and Shaw 2007). It has been demonstrated that PINK1 phosphorylates Miro1 on Ser156 to induce PARKIN and proteasomal degradation of it, releasing Milton/Kinesin complex from mitochondrial surface and leading to arrest dysfunctional mitochondria motility in neurons (Liu et al. 2012; Xinnan; Wang et al. 2011). This is considered as an initial quarantining step prior to mitophagy. See Fig. 3c.

Also, PINK1/PARKIN pathway appears to selectively affect the dynamics of dysfunctional mitochondria within the cell through the regulation of fusion/fission machinery as a mitochondrial quality control measure (Chen and Dorn 2013; Poole et al. 2008; Yu et al. 2015). In mammals, mitochondrial fusion was identified to be regulated by three membrane-bound GTPases, including mitofusins (Mfn) 1 and 2 for OMM fusion and optic atrophy 1 (OPA1) for IMM fusion (Chen et al. 2003; Song et al. 2007). PINK1 was reported to phosphorylate Mfn2 at Thr111 and Ser442 to induce PARKIN and subsequent proteasomal degradation of Mfn2 (Chen and Dorn 2013). It seems that PINK1/PARKIN pathway inhibits mitochondrial fusion through the degradation of Mfn1/2 and prevents damaged mitochondria fusing with healthy mitochondria. Such isolation of dysfunctional mitochondria from the healthy mitochondrial network is considered as an essential step prior to induction of mitophagy (Gegg et al. 2010; Poole et al. 2010). See Fig. 3b.

Although PINK1/PARKIN pathway affects mitochondrial dynamics and trafficking by proteasomal degradation of specific mitochondrial outer membrane proteins (OMM proteins with K48-linked ubiquitin chains), it appears to target the entire mitochondria for autophagic degradation by selective recruitment of adaptor proteins to other mitochondrial outer membrane substrates (OMM proteins with K63-linked
ubiquitin chains) (Narendra et al. 2012). There is a leading hypothesis that the ubiquitin chains attached by PARKIN to some OMM proteins or mitophagy receptors including BNIP3L (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like), FUNDC1 (FUN14 domain-containing protein 1), and BCL2L13 (BCL2-like 13) serve as a positive signal for several different proteins such as p62/SQSTM1 (Sequestosome 1), NBR1 (Neighbor of BRCA1), NDP52 (Nuclear dot protein 52 kD), and OPTN (Optineurin) and recruit them to OMM (Gao et al. 2015; Geisler et al. 2010; Heo et al. 2015; Liu et al. 2012a, b; Otsu et al. 2015). These proteins function as adaptor proteins and bind both to ubiquitin chains and LC3/GABARAP (Gamma-aminobutyric acid receptor-associated protein) family members, which in turn recruit different protein complexes to growing isolation membranes that expand alongside mitochondria. The mechanisms involved in phagophore expansion are probably mediated by phagosome membrane uptake through the interaction of LC3/GABARAP with the autophagosome membrane and autophagy protein complex, ATG12-ATG5-ATG16L (Kabeya et al. 2004; Yang and Klionsky 2010). On the other hand, recent studies have uncovered that three mitochondrial localized proteins including RabGAPs, TBC1D15 (TBC1 Domain Family Member 15), and TBC1D17 (TBC1 Domain Family Member 17) bind to the mitochondrial outer membrane protein Fission1 via interaction with LC3/GABARAP and leads to positive regulation of autophagosomal membrane engulfment of mitochondria. The autophagosome then fuses with a lysosome, leading to degradation of the dysfunctional mitochondria by the proteases and lipases that reside in lysosomes (Shen et al. 2014; Yamano et al. 2014). See Figs. 1c, 3b, and 4.

**DJ-1**

Mutations in the *DJ-1* gene are known to be associated with rare cases of autosomal recessive PD (1% of early-onset PD) (Bonifati et al. 2003). Clinically, patients affected with *DJ-1* mutations were found to have an early asymmetric development of dyskinesia, hyperreflexia, rigidity, and tremor, with later psychiatric symptoms including, psychotic disturbance, cognitive decline (uncommon), anxiety, and also a good response to l-DOPA (similar to clinical and phenotypic features of patients with PARKIN and PINK1 mutations) (Abou-Sleiman et al. 2003; Annesi et al. 2005; Bonifati et al. 2003; Ibáñez et al. 2006). *DJ-1* encodes a protein involved in transcriptional regulation and antioxidative stress reaction within the neuronal cells (Ottolini et al. 2013). Under normal condition, subcellular localization investigations have revealed that DJ-1 is predominantly located in the cytoplasm and to a lesser extent in the nucleus and mitochondria (Junn et al. 2009; Nagakubo et al. 1997; Zhang et al. 2005). However, Junn et al. (2009) recently observed that DJ-1 translocation into the nuclear compartment is enhanced in response to oxidative stress (Junn et al. 2009). It has proven that the activation and subsequently nuclear localization of DJ-1 protects cells against reactive oxygen species (ROS), which is followed by self-oxidation at cysteine 106 (C106), a highly susceptible residue to oxidative stress (oxidative stress sensor residue), and formation of cysteine–sulfonic acid (SOH, SO2H) upon exposure to oxidative stress (Canet-Avilés et al. 2004; Kim et al. 2012; Kinumi et al. 2004). In addition, several studies have reported that under excessive oxidative stress conditions, DJ-1 is oxidized as SO3H at cysteine 46 (C46), cysteine 53...
Cysteine 106 (C106) residues, which is an inactive form of DJ-1 observed in brains of patients with PD and Alzheimer’s disease (Bandopadhyay et al. 2004; Choi et al. 2006; Kinumi et al. 2004; Zhou et al. 2006).

In response to oxidative stress, DJ-1 in its oxidized form, acts as a neuroprotective transcriptional coactivator and regulates the activity of several DNA-binding transcription factors (TFs) including nuclear factor erythroid-2-like 2 (NFE2L2), polypyrimidine tract-binding protein-associated splicing factor (PSF) and p53 (Clements et al. 2006; Fan et al. 2008a, b; Zhong et al. 2006). Several lines of evidence obtained from separate studies suggesting that the TFs whose activity is regulated by DJ-1 may trigger multiple cytoprotective pathways against oxidative stress and subsequent neuronal cell death (Martinat et al. 2004; Venderova and Park 2012).

Investigation of ROS metabolism in human umbilical vein endothelial cells (HUVECs) has shown that NFE2L2 serves as a master TF for cellular antioxidant functions and detoxification responses (Kinumi et al. 2004). Without oxidative stresses, NFE2L2 is localized in the cytoplasm and interacts with KEAP1, which is an inhibitor protein and promotes ubiquitin–proteasome degradation of NFE2L2. Upon oxidative stress, DJ-1 disrupts the NFE2L2-KEAP1 interaction to stabilize NFE2L2, leading to translocation of NFE2L2 into the nucleus (Clements et al. 2006). This process is essential for the expression of several detoxifying and antioxidant enzyme genes through the binding of NFE2L2 to the antioxidant response elements (AREs) in their promoters, and thereby increasing neural protection against DNA damage and apoptosis (Im et al. 2012; Kensler et al. 2007; Vargas and Johnson 2009).

Tyrosine hydroxylase (TH) is a rate-limiting enzyme for dopamine synthesis and its deficiency contributes to the typical clinical symptoms of PD. Several protein-interaction studies have suggested that DJ-1 and PSF bind and transcriptionally regulate the human TH promoter (Ishikawa et al. 2009, 2010). Western blot analysis of SUMO species using immunoprecipitated PSF has demonstrated that PSF is sumoylated in human dopaminergic neuroblastoma SH-SY5Y cell lines. Sumoylation of PSF leads to the recruitment of histone deacetylase (HDAC) 1 to TH promoter and increase deacetylation of the TH promoter-bound histones, which subsequently results in the loss of TH expression and dopamine production. It has proven that DJ-1 positively regulates human TH gene expression by blocking the sumoylation of PSF and subsequently preventing HDAC1 recruitment to the TH promoter (Xu et al. 2005; Zhong et al. 2006). In addition, DJ-1 has been shown to stimulate vesicular monoamine transporter 2 (VMAT2) activities by...
transcriptional upregulation of VMAT2 gene and by direct binding to VMAT2 protein. VMAT2 is an integral membrane protein that transports cytosolic dopamine, a highly reactive molecule, into synaptic vesicles to avoid the effect of autoxidized dopamine on neuronal cell degeneration. These findings support the theory that stimulating activity of DJ-1 toward VMAT2 contributes to the protective reaction against dopamine toxicity (Ishikawa et al. 2012).

The p53 functions as a tumor suppressor protein and plays major roles in suppression of cell growth in response to stress conditions by induction of either cell cycle arrest or apoptosis. Human topoisomerase I-binding protein (Topors) is defined as a rate-limiting factor in the regulation of p53 activity. Under stress conditions, Topors acts as a coactivator of p53 and induces cell cycle arrest or apoptosis through enhancing the transcription of p53 downstream genes including Bax and p21 (Hofseth et al. 2004; Lin et al. 2005). DJ-1 has been shown to inhibit the induction of apoptosis by p53 through inhibition of Topors activity. It has also been reported that DJ-1 directly binds to the DNA-binding region of p53 and represses p53 transcriptional activity on Bax and p21 promoters, leading to neural cell cycle progression (Fan et al. 2008a, b; Kato et al. 2013).

It is suggested that DJ-1 involves within the cytoprotective pathways against oxidative stress and mutations in it cause the progressive apoptotic death of neuron cells, which can eventually lead to early onset of PD symptoms.

**LRRK2**

Mutation in *Leucine-rich repeat kinase 2 (LRRK2)* gene is known as one of the common genetic cause of PD (Healy et al. 2008); they are responsible for at least 4% of autosomal dominant forms of familial PD typically associated with late onset and are also found in 1% of sporadic PD worldwide (Di Fonzo et al. 2005; Gilks et al. 2005; Nichols et al. 2005). Patients affected with *LRRK2* mutations exhibit a broad spectrum of clinical and phenotypic features including bradykinesia, muscular rigidity, tremor, cognitive decline, moderate dementia, olfactory deficits, hallucinations, sleep disturbance, orthostatic hypotension, and appreciable response to L-DOPA (Alcalay et al. 2009; Wszolek et al. 1995). However, several studies have reported that Lewy bodies (the pathological hallmarks of PD) are absent in some PD patients affected with *LRRK2* mutations (Funayama et al. 2005). The *LRRK2* gene encodes a large multifunction with important kinase activities. Some PD-associated mutations to *LRRK2* result in increased kinase activity of the protein, which may suggest a toxic gain of function mechanism. Wang et al. (2012) found that *LRRK2* regulates mitochondrial dynamics by interacting with a number of key regulators of mitochondrial fission/fusion, on mitochondrial membranes (Xinglong Wang et al. 2012). Wild-type *LRRK2* gene expression studies in human neuronal cell lines concluded that endogenous LRRK2 directly interacts with dynamin-related protein 1 (DRP1), a mitochondrial fission protein, increasing DRP1 phosphorylation and mitochondrial fission (Saez-Atienzar et al. 2014; Xinglong; Wang et al. 2012). The LRRK2-DRP1 interaction was enhanced by overexpressing wild-type LRRK2 and by LRRK2 PD-associated mutations (Su and Qi 2013; Xinglong; Wang et al. 2012). Also, it has been recently shown that LRRK2 modulates mitochondrial fusion regulators Mfn1/2 and OPA1 activities by interacting with them at the mitochondrial membrane. Additionally, decreased levels of reactive OPA1 have been observed in sporadic PD patients carrying some LRRK2 pathogenic mutations (Stafa et al. 2013). Increased kinase activity of LRRK2 results in aberrant increased mitochondrial fragmentation which was associated with mitochondrial dysfunction, increased ROS production from mitochondrial complexes, and subsequently enhanced susceptibility to oxidative stress. These observations suggest that altered mitochondrial fission/fusion which is caused by mutations in *LRRK2* gene is an important factor in the pathogenesis of PD.

**HTRA2/OMI**

*High-temperature requirement A2 (HTRA2/OMI)* is another attractive candidate gene for PD that encodes a serine protease localizing to the mitochondrial intermembrane space (IMS). A heterozygous G399S missense mutation in the coding sequence of the gene was first identified in four German patients with PD (Strauss et al. 2005). However, evidence for the pathogenesis of *HTRA2/OMI* in PD has been further supported by whole exome sequence analyses in patients with PD from the Taiwan, Pakistan, Mexico, and in affected infants, born of consanguineous parents of Druze and Ashkenazi origins (Lin et al. 2011; Mandel et al. 2016; Oláhová et al. 2017). Also, some phenotypic similarities with parkinsonian features, including motor abnormalities and the progressive neurodegeneration in some brain regions, especially in the striatum were observed in HTRA2/OMI loss-of-function mice, indicating that HTRA2/OMI can serve a neuroprotective function (Jones et al. 2003; Martins et al. 2004). Loss of HTRA2/OMI protease activity in OMI-knockout mouse embryonic fibroblast cells showed increased mitochondrial DNA mutation, decreased mitochondrial membrane potential, altered mitochondrial morphology, and reduced mitochondrial density (Kang et al. 2013; Rathke-Hartlieb et al. 2002). It has been proposed that HTRA2/OMI is involved in the quality control of the proteins targeted for mitochondrial IMS by proteolysis of misfolded and damaged proteins, which is induced upon proteotoxic stress (Walle et al. 2008). In addition, it has been demonstrated that in mammalian cells HTRA2/OMI is released from mitochondria to the cytosol in response to apoptotic...
stimuli and induces apoptosis through interaction and proteolytic elimination of inhibitor of apoptosis proteins including c-IAP1 and XIAP (Suzuki et al. 2001; Yang et al. 2003). However, under nonapoptotic conditions, the HTRA2/OMI is restricted to the mitochondrial IMS and is also implicated in mitochondrial protein quality control (Cilenti et al. 2014; Kieper et al. 2010). These findings provided a link between mutations in HTRA2/OMI gene and mitochondrial dysfunction which is associated with neurodegeneration seen in some patients with PD (Bogaerts et al. 2008).

**CHCHD2**

More recently, evidence for the role of mitochondrial dysfunction in the pathogenesis of Parkinson’s disease was further confirmed, based on the identification of heterozygous mutation in the coiled-coil-helix-coiled-coil-helix domain 2 (CHCHD2) gene using whole genome analysis in a Japanese family with autosomal dominant Parkinson disease. Clinical features of the patients usually include PD typical symptoms such as tremor, bradykinesia, rigidity, postural instability, and a good response to l-DOPA treatment (Funayama et al. 2015). This gene encodes a protein that is active in two cellular compartments including mitochondria and nucleus and is involved in the regulating mitochondrial metabolism under conditions of oxygen stress (Aras et al. 2015). In normal conditions, CHCHD2 is predominantly present within the mitochondrial intermembrane space (MIS) and binds to the subunit 4 of cytochrome C oxidase (COX4), which is necessary for optimal COX activity. COX is the last enzyme present in the electron transfer chain and plays a key role in the process of respiration within the mitochondrial membrane. In fact, its interaction with CHCHD2 plays a key role in maintaining energy balance inside the neurons under hypoxic conditions, by increasing COX4 efficiency and producing appropriate energy in the form of ATP via oxidative phosphorylation (Aras et al. 2013). Consistent with these observations, knockdown of CHCHD2 expression in human fibroblasts led to mitochondrial dysfunctions through reduced COX4 activity, oxygen consumption, and mitochondrial membrane potential, and increased ROS and mitochondrial fragmentation. Also, CHCHD2 functions as a master transcription factor to cope with oxidative stress. DNA-binding assays indicated that CHCHD2 binds to the proximal promoter of COX4 gene as an oxygen responsive element (ORE) to increase its transcription. In addition, these studies revealed that CHCHD2 participates in a positive feedback loop and increases its expression through binding to ORE in its own promoter. It has been proven that although, a small portion of CHCHD2 is present in the nucleus under normal conditions, during the course of continuous oxidative stress the translocation of CHCHD2 into the nucleus is further stimulated in order to promote itself and COX gene transcription as anti-hypoxic responses (Aras et al. 2015, 2013). Furthermore, it has been reported that CHCHD2 binds to the Bcl-xL and regulates its activity in order to inhibit induction of apoptosis by the accumulation of Bax on the mitochondrial membrane under oxidative stress conditions (Liu et al. 2015). It is proposed that mutations in CHCHD2 gene impair neuroprotection responses against hypoxic stress conditions through disruption of mitochondrial metabolism, thereby increasing the ROS level and also induction of apoptosis by Bax.

**VPS13C**

Recently, whole genome studies in the field of Parkinsonism revealed that mutations in vacuolar protein sorting 13C (VPS13C) are associated with the development of autosomal recessive early-onset forms of PD. Clinically, patients affected with VPS13C mutations show the rapid and severe progression of bradykinesia, tremor, cognitive decline, and autonomic dysfunctions as well as a good response to l-DOPA treatment at the early stage (Lesage et al. 2016; Nalls et al. 2014). It has been proven that VPS13C encodes a member of a family of vacuolar protein sorting 13 (VPS13) (Velayos-Baeza et al. 2004). Currently, the molecular pathway(s) underlying how mutations in VPS13C cause PD remain unknown. However, in vitro experiments on human cell models showed that VPS13C is located on the outer mitochondrial membrane. Also, knockdown of VPS13C in the animal cell models is markedly associated with lower mitochondrial membrane potential, increased ROS, mitochondrial fragmentation, abnormal mitochondrial morphology, and upregulation of the expression of PARKIN and PINK1 genes in response to toxin-induced mitochondrial dysfunction. It is believed that VPS13C cooperates with PARKIN/PINK1 pathway and contributes to the selective delivery of damaged mitochondria cargo to the lysosome (Lesage et al. 2016; Schreglmann and Houlden 2016). In fact, it is proposed that mutations in VPS13C gene may lead to the increased amount of ROS and dysfunctional mitochondria and ultimately trigger neuronal cell death.

**UCHL1**

*Ubiquitin C-terminal hydrolase L1 (UCHL1)* encodes a highly neuron-specific member of a gene family whose products function in the ubiquitin recycling pathway by hydrolyzing polymeric ubiquitin chains into monomers. The presence of UCHL1 in Lewy bodies and its function in the proteasome pathway suggested that it could be a compelling PD candidate gene. A heterozygous I93M mutation in the UCHL1 gene was found in affected members of a German family with autosomal dominant Parkinson disease. Clinical manifestations such as tremor,
muscular rigidity, bradykinesia, and postural instability, as well as good response to l-DOPA treatment, were typical for PD (Healy et al. 2004; Leroy et al. 1998). In vitro analysis showed that the mutant allele of \textit{UCHL1} had ~50\% reduced hydrolytic activity compared with the wild-type enzyme (Kensler et al. 2007; Nishikawa et al. 2003). Additionally, reduced levels of monoubiquitin in neurons were detected among the mice with neuroaxonal dystrophies, in which the function of \textit{UCHL1} was lost (Saigoh et al. 1999). However, in neuronal cell culture and mice, the expression of \textit{UCHL1} demonstrated an increase in the level of ubiquitin within the neurons (Osaka et al. 2003). These findings led to conclude that \textit{UCHL1} may play a role in ubiquitin stability within neurons, which is critical for ubiquitin–proteasome system and neuronal survival (Meray and Lansbury 2007).

**GBA**

Several studies reported Parkinsonism in patients with Gaucher’s disease (GD), a lysosomal storage disorder caused by mutations in \textit{Glucocerebrosidase (GBA)} gene (Grabowski 2008). Moreover, in some families affected with GD, several relatives of the probands developed Parkinsonism, many of whom were obligate heterozygous carriers of the \textit{GBA} mutant alleles. The patients had an atypical onset of PD, including cognitive defects and hallucination. However, the disorder was progressive, and later they developed asymmetric manifestation of tremor, muscular rigidity, bradykinesia, and postural instability. It has been suggested that some \textit{GBA} mutations may be a risk factor for the development of Parkinsonism in these families (Goker-Alpan et al. 2004; Sidransky 2004). The link between \textit{GBA} and PD was also supported by neuropathology studies, showing dopaminergic neuronal dysfunction with widespread pathologies of \textit{α}-synuclein and Lewy body in patients with homozygous and heterozygous \textit{GBA} mutation (Kono et al. 2007). In addition, detailed biochemical studies showed significant decrease in glucocerebrosidase enzyme (GCase) activity and increase in \textit{α}-synuclein accumulation in PD brains, with \textit{GBA} mutations. GCase catalyzes the breakdown of sphingolipid glucosylceramide to ceramide and glucose within lysosomes and reduced enzyme activity and mutant protein may lead to impaired lysosomal protein degradation and increased exosomal release of \textit{α}-synuclein and formation of its related toxic aggregates (Lin and Farrer 2014; Mazzulli et al. 2011; Schapira and Jenner 2011; Xu et al. 2011). See Fig. 1b. However, in line with these findings, most recent studies reported that the homozygous or heterozygous \textit{GBA} mutations lead to a 20- to 30-fold increase in the risk of PD and 5–10\% of PD patients have mutations in \textit{GBA} gene (Velayati et al. 2010).

**ATP13A2**

Originally, ATP\textit{ase type 13A2 (ATP13A2)} has been reported associated with Kufor–Rakeb syndrome (KRS), which is a severe early-onset PD, inherited in an autosomal recessive manner. Clinically, patients affected with KRS tend to show progressive brain atrophy, tremor, rigidity, bradykinesia, dystonia, dementia, cognitive impairment, depression, supranuclear gaze palsy, and a better response to l-DOPA (Al-Din et al. 1994; Crosiers et al. 2011; Williams et al. 2005). ATP13A2 gene belongs to the 5\textit{P}-type subfamily of ATPase and encodes a lysosomal transmembrane protein that is mainly expressed in the brain. To date, the biochemical findings of ATP13A2 represent a class of proteins with unassigned function and substrate specificity (Dehay et al. 2012; Murphy et al. 2013; Ramirez et al. 2006). However, several different studies on the cultured KRS-patient dermal fibroblasts and other types of ATP13A2-deficient cell lines such as human neuroblastoma SHSY5Y cells determined that loss of functional ATP13A2 leads to instability of the lysosomal membrane and subsequently impaired lysosomal proteolysis function, which is essential to the lysosomal-mediated proper protein and mitochondrial quantity and quality control pathways within neurons (Dehay et al. 2012; Gusdon et al. 2012; Tofaris 2012); see Fig. 1d. These defects are tightly associated with pathogenic accumulation of \textit{α}-synuclein and mitochondrial dysfunction, resulting in decreased ATP production and increased intracellular levels of ROS that contribute to the neuronal cell death (Gitler et al. 2009; Grünewald et al. 2012; Kong et al. 2014). In addition, several other studies have identified abnormal accumulation of manganese (\textit{Mn}^{2+}) and zinc (\textit{Zn}^{2+}) in the brain and cerebrospinal fluid of PD patients affected with ATP13A2 mutations (Fukushima et al. 2011; Hozumi et al. 2011; Jiménez-Jiménez et al. 1992). Moreover, Tan et al. (2011) found that overexpression of ATP13A2 in cultured neuronal cells exposed to Mn^{2+} reduced intracellular Mn^{2+} concentrations and protected cells from subsequent apoptosis (Tan et al. 2011). It is believed that ATP13A2 protects cells from metal toxicity by providing homeostasis of Mn^{2+} and Zn^{2+} (the significant environmental risk factors for PD) within neurons (Guilarte 2010; Pals et al. 2003; Rentschler et al. 2012).

It is speculated that mutations in ATP13A2 may disrupt normal intracellular homeostasis of divalent cations and lead to lysosomal and mitochondrial defects within neurons and ultimately significant neurodegeneration that is the distinguishing pathological feature of PD.

**PLA2G6**

\textit{Phospholipase A2 group 6 (PLA2G6)} has been characterized as the causative gene for different neurodegenerative
diseases, including infantile neuroaxonal dystrophy (INAD), neurodegeneration with brain iron accumulation (NBIA), and Karak syndrome. However, recent genetic analysis of affected families from India, Iran, and Pakistan has been reported that mutations in the PLA2G6 gene are responsible for early-onset dystonia-Parkinsonism with autosomal recessive inheritance (Morgan et al. 2006; Paisán-Ruiz et al. 2009; Paisán-Ruiz et al. 2010; Sina et al. 2009). The main clinical features of the patients affected with PLA2G6 mutations are tremor, muscular rigidity, bradykinesia, dystonia, brain atrophy, dementia, visual disturbance, good response to l-DOPA therapy at first, and later l-DOPA-induced dyskinesia (Paisán-Ruiz et al. 2009; Sina et al. 2009; Yoshino et al. 2010). It has been proven that PLA2G6 gene encodes calcium-independent group 6 phospholipase A2 enzyme, which hydrolyzes the sn-2 ester bond of the membrane glycerophospholipids to yield free fatty acids and lysophospholipids (Balsinde and Balboa 2005). This function has profound effects on the repair of oxidative damage to the cellular and subcellular membrane phospholipids, membrane fluidity, and maintenance of membrane permeability or iron homeostasis (Balsinde and Balboa 2005; Shinzawa et al. 2008). In addition, Beck et al. (2015, 2016) demonstrated that knocking out the PLA2G6 gene in mice leads to defects in remodeling of mitochondrial inner membrane and presynaptic membrane and subsequently causes mitochondrial dysfunction, age-dependent degeneration of dopamine nerve terminals, synaptic dysfunction, and significant iron accumulation in the brains of PLA2G6 knockout mice (Beck et al. 2016, 2015). These findings suggest that impairment of the dopaminergic nervous system and brain iron accumulation caused by mutations in the PLA2G6 gene can be considered as a pathogenic mechanism in sporadic and familial PD (Kauther et al. 2011).

VPS35

In 2011, pathogenic mutations in the vacuolar protein sorting 35 (VPS35) gene have been reported as novel causes of autosomal dominant PD, by application of whole exome sequencing to a large Swiss kindred representing late-onset tremor-predominant Parkinsonism (Vilariño-Güell et al. 2011). The main phenotypes associated with VPS35 mutations in this kindred were tremor, dyskinesia, rigidity, dystonia, and good response to l-DOPA with rare cognitive or psychiatric symptoms (Kumar et al. 2012). Recent studies indicate that VPS35 gene encodes a core component of the retromer cargo-recognition complex and plays a critical role in cargo retrieving pathway from the endosome to the trans-Golgi network (TGN) (Fuse et al. 2015; Tsika et al. 2014; Zavodszyk et al. 2014). It has been proven that Cation-independent mannose 6-phosphate receptor (CI-MPR) is one of the best characterized cargo proteins of the retromer complex, which is involved in the trafficking of lysosomal proteases, such as the cathepsin D (CTSD), to lysosomes (Bugarcic et al. 2011; Choy et al. 2012; Seaman 2007). Under normal conditions, CTSD is specifically modified by attaching mannose 6 phosphates (M6P) residues to its signal peptide (M6P-CTSD) inside the TGN (Miura et al. 2014). Subsequently, M6P-CTSD is recognized by the CI-MPR and is trafficked from the TGN to the endosome. Inside the endosome, CTSD is activated by proteolytic cleavage of the signal peptide and then is released for further traffic to the lysosome. Ultimately, retromer retrieves free CI-MPRs from the endosome to the TGN, in which they can be involved in further cycles of CTSD trafficking to the lysosome (Laurent-Matha et al. 2006; Miura et al. 2014). It seems that dominant negative mutations in VPS35 cause retromer complex dysfunction and lead to decreased delivery of CTSD to the lysosome and subsequently impaired lysosomal proteolysis function which is essential to the lysosomal-mediated proper protein quality control pathways (Follett et al. 2014; Fuse et al. 2015; Hernandez et al. 2016). In addition, Miura et al. (2014) demonstrated that knocking down the VPS35 gene in Drosophila leads to the toxic accumulation of the α-synuclein within the neurons which can further support the role of VPS35 in the pathogenesis of PD (Miura et al. 2014). See Fig. 5.

FBXO7

In 2008, F-box protein 7 (FBXO7) was identified as a novel PD causative gene by a genome-wide linkage analysis in a large Iranian family, affected with autosomal dominant early-onset PD (Shojaei et al. 2008). Also, homozygote and compound heterozygote loss-of-function mutations in FBXO7 have been reported in Italian and Dutch families. Affected members usually showed tremor, rigidity, bradykinesia, postural instability, hyperreflexia, saccadic eye movement with normal cognition, and appreciable response to l-DOPA (Di Fonzo et al. 2009a, b). To date, the precise mechanism by which FBXO7 contributes to neurodegeneration process remains poorly defined. However, it has been proven that FBXO7 functions as a molecular scaffold in the formation of protein complexes. FBXO7 has been reported to mediate the formation of SCF (Skp1, Cullin1, F-box protein) ubiquitin ligase complexes, and plays roles in the ubiquitin–proteasome degradation pathway (Nelson et al. 2013). In addition, recent invito analyses have identified that FBXO7 physically interacts with PARKIN. In this regard, biochemical findings in Drosophila showed that overexpression of wild-type FBXO7 suppresses mitochondrial disruption and also neurodegeneration process in PARKIN mutants, confirming that they share a common role in mitochondrial biology (Burchell et al. 2013; Zhou et al. 2016). As a result, it is assumed that FBXO7 functions in a common pathway
Fig. 5  

**a** VPS35 is a core component of the retromer cargo-recognition complex and plays a critical role in cargo retrieving pathway from the endosome to the trans-Golgi network (TGN); **b** mutations in VSP35 cause retromer complex dysfunction and lead to decreased delivery of CTSD to the lysosome and subsequently impaired lysosomal proteolysis function; Refer to the text for more explanations.
with PARKIN and PINK1 to induce selective autophagic clearance (mitophagy) in response to damaged mitochondria and pathogenic mutations in FBXO7 may interfere with this pathway (Conedera et al. 2016; Randle and Laman 2017; Vingill et al. 2016).

**EIF4G1**

Originally, mutations in *Eukaryotic translation initiation factor 4 gamma, 1 (EIF4G1)* gene were identified in a large French family with autosomal dominant PD and confirmed in several families from the United States of America (USA), Canada, Ireland, Italy, and Tunisia. Clinically, affected individuals with *EIF4G1* mutations show late onset of asymmetric resting tremor, bradykinesia, muscle rigidity, with preserved cognition and good response to L-DOPA treatment (Chartier-Harlin et al. 2011). *EIF4G* gene family encodes a large scaffold protein that functions as a key initiation factor in mRNA translation and protein synthesis within eukaryotic cells by recruiting the multisubunit translation initiation factor complex at the 5′ cap of mRNAs (Ali et al. 2001). *EIF4G1* is a member of *EIF4G* gene family which selectively regulates the cap-dependent translation initiation of a subset of mRNAs encoding proteins function in mitochondrial activity, cellular bioenergetics, cellular growth, and proliferation in response to different cellular stresses (Ramírez-Valle et al. 2008; Silvera et al. 2009). Also, it has been reported that the high levels of EIF4G1 are associated with malignancy in a significant number of human breast cancers suggesting that overexpression of EIF4G1 may specifically increase cell proliferation and prevent autophagy in some human cancers (Schneider and Sonenberg 2007). Moreover, the loss of mitochondrial membrane potential and biogenesis has been observed in *EIF4G1*-silenced cells subjected to hydroperoxide treatment. It has been proposed that mutations in *EIF4G1* impair the mRNA translation initiation in PD. In fact, such mutations alter the translation of existing mRNAs essential to neuronal cell survival and their abilities to rapidly and dynamically respond to stress (Chartier-Harlin et al. 2011).

**GIGYF2**

A genome-wide linkage analysis by use of 400 dinucleotide markers in a sample of sib pairs with late-onset autosomal dominant Parkinsonism found linkage to the 2q36–q37 chromosomal region (Pankratz et al. 2002). The marker with the highest linkage score (D2S206, LOD 5.14) was within the *Grb10-Interacting GYF Protein-2 (GIGYF2)* gene region (Tan and Schapira 2010). Later sequence analysis of the *GIGYF2* gene region in 12 unrelated familial PD patients from Italy and France revealed seven different heterozygous mutations in the GIGYF2 gene, while these mutations were absent in controls (Lautier et al. 2008). However, there is some controversy surrounding the role of GIGYF2 gene in the pathogenesis of PD, since several recent studies did not provide strong evidence for the association between *GIGYF2* gene mutations and PD (Bras et al. 2008; Di Fonzo et al. 2009b; Guo et al. 2009).

Studies in cultured cells, as well as yeast two-hybrid analysis, revealed that GIGYF2 may be recruited to activated-IGF-I/Insulin receptors through binding to the N-terminus of Grb10 (Giovannone et al. 2003). Grb10 is recruited to tyrosine phosphorylated IGF-I/insulin receptors, in response to IGF-1/insulin stimulation (Dey et al. 1996; Hansen et al. 1996). It has been proven that Grb10 serves as an adaptor protein between NEDD4 and IGF-1 receptor and triggers ligand-induced ubiquitination and subsequent degradation of the IGF-I/insulin receptor (Langlais et al. 2004; Vecchione et al. 2003). Also, Overexpression Grb10 gene in mice leads to postnatal growth retardation which further supports a role for the Grb10 protein in negatively regulating cell growth via the modulation of IGF-I/insulin receptor signaling (DuFresne and Smith 2005; Shiura et al. 2005). In contrast, expression of GIGYF2 in cultured cells showed a significant increase in IGF-1-stimulated receptor tyrosine phosphorylation (Higashi et al. 2010). In fact, it is postulated that GIGYF2 binding to Grb10 results in a significant increase in IGF-I/insulin receptor signaling pathway. In addition, a report showed that heterozygous GIGYF2+/− mice develop adult-onset neurodegeneration, indicating that GIGYF2 gene dysfunction may have an important role in neurodegeneration process in the central nervous system (CNS) (Giovannone et al. 2003, 2009).

**ATXN2**

During the last decade, researches in the field of Parkinsonism have described an association between CAG repeat expansions within the coding region of Ataxin-2 (*ATXN2*) gene and dominantly inherited familial forms of PD (Gwinn–Hardy et al. 2000; Payami et al. 2003). Molecular genetic analyses in affected families have reported that normal *ATXN2* alleles contain 14–31 CAG repeats, whereas pathologic alleles may carry expanded CAG repeats ranging in size from 35 to more than 200 (Lu et al. 2004). Clinical examinations suggest that cerebellar ataxia is usually the predominant symptom among patients. However, they often show some parkinsonian symptoms such as tremor, rigidity, bradykinesia, saccadic eye movement disorder, and good response to L-DOPA (Lu et al. 2004; Ragothaman et al. 2004). Although the biochemical function of ATXN2 is currently unknown, molecular studies in Drosophila suggest that ATXN2 may play roles in transport, stability, and translation regulation of a subset of mRNAs within neurons (Al-Ramahi et al. 2007; Halbach et al. 2015; Satterfield and Pallanck 2006). It seems that CAG repeat expansions within
the coding sequences of ATXN2, resulting in the expansion of a polyglutamine (poly Q) tract in the ATXN2 may cause translational dysregulation of particular mRNAs and subsequently trigger the degeneration of dopaminergic neurons within the brain (Nkiliza et al. 2016; Satterfield and Pallanck 2006).

DNAJC6

Autosomal recessive inheritance of mutations in the DNAJC6 gene linked to juvenile-onset (< age 20) atypical Parkinsonism (PARK 19) has been reported. Disease progression in affected individuals was rapid, leading to a wheelchair-bound state within 10 years of onset. Response to l-DOPA was poor or absent and additional atypical manifestations such as mental retardation, seizures, dystonia, and pyramidal signs were observed (Edvardson et al. 2012; Koroglu et al. 2013). The DNAJC6 gene codes for a brain-specific auxilin protein (Olgiati et al. 2016) which plays a role in the presynaptic endocytosis of clathrin-coated vesicles. The impairment of this pathway impacts on the formation of new vesicles at the presynaptic terminal (Kononenko and Haucke 2015). Variable phenotypes have been observed in PD patients expressing homozygous DNAJC6 mutations with the onset of parkinsonian features occurring between the 3rd and 5th decade of life, disease progression being slower and with better responses to dopaminergic therapies. This separates patients markedly from PARK19 to be categorized as early-onset PD (< age 45) and suggests that some milder pathogenic mutations in the DNAJC6 gene may allow for reduced auxilin expression (Olgiati et al. 2016).

SYNJ1

Mutations in the SYNJ1 gene have been reported to cause juvenile-onset atypical Parkinsonism (PARK20) through autosomal recessive inheritance. Typical features occurring at a young age include bradykinesia, tremor, dystonia, and apraxia of eyelid opening (ALO) as well as cognitive decline and generalized seizures in some patients (Quadri et al. 2013; Krebs et al. 2013; Olgiati et al. 2014). The SYNJ1 gene encodes synaptojanin-1, a presynaptic phosphoinositide phosphatase protein which has a role in the regulation of synaptic vesicle endocytosis, important in the recycling of proteins. Animal study has shown that mutations in the Sac phosphatase domain of SYNJ1 led to Parkinson’s-like neurological features and an increase in the levels of PD-associated proteins; auxilin, which has a similar role to synaptojanin-1 in endocytosis and PARKIN. The impairment of the endocytic recycling pathway led to an accumulation of proteins at synaptic terminals and it was observed to selectively result in dystrophic dopaminergic axon terminals in the dorsal striatum. Phenotypic presentation in the animals studied provided strong evidence for a link between SYNJ1 mutations and juvenile-onset PD, while elevated levels of auxilin and PARKIN suggesting an interaction with other PD-associated genes as a potential pathological mechanism (Cao et al. 2017).

DNAJC13

The DNAJC13 gene encodes an endosomal protein involved in clathrin coating of vesicles and as such is involved in intracellular transport. Mutations have been reported through a dominant inheritance leading to PD in patients, characterized by α-synuclein positive Lewy bodies, with age of onset being between 40 and 83 years. Disease progression is slow with duration noted at between 8 and 17 years and l-DOPA only effective in earlier stages (Vilarino-Guell et al. 2014; Appel-Cresswell et al. 2014; Gustavsson et al. 2015; Ross et al. 2016). It has been hypothesized that the accumulation of α-synuclein is a direct result of impaired intracellular transport due to toxic gain-of-function mutations in the DNAJC13 gene. This has been demonstrated in vivo using Drosophila models which linked mutant DNAJC13 to increased levels of insoluble α-synuclein in the fly head, degeneration of dopaminergic neurons, and age-dependent locomotor deterioration (Yoshida et al. 2018).

PARK3, PARK 10, PARK 12

Several different genome-wide linkage analyses (GWLA) have been performed on the large groups of PD-affected families by genotyping of most popular genetic polymorphic markers including microsatellites and single-nucleotide polymorphisms (SNPs) (Funayama et al. 2015; Moghadam et al. 2017; Ott et al. 2015). Because PD is considered as a complex disease and causative loci may have different types of inheritance, the model of its inheritance is unknown (Keller et al. 2012). Therefore, linkage analysis based on model-free method would be more effective to map the loci responsible for the disease (Lander and Kruglyak 1995). In this approach, the PD-affected sibs inherited significantly more common alleles (identical by descent; IBD) at polymorphic loci linked to the disease than expected by chance (the expected probabilities of sharing 2, 1, and 0 IBD alleles for affected sib pairs at the disease locus will not be 0.25, 0.5, and 0.25, respectively) (Kruglyak et al. 1996; Nowak et al. 2012). As illustrated in Table 1, using model-free GWLA, three responsible loci for the PD have been mapped (PARK3 on 2p13, PARK10 on 1p32, and PARK12 on Xq21-q25), but the causative genes have not yet been identified (DeStefano et al. 2002; Hicks et al. 2002; Pankratz et al. 2003).
Sporadic PD

In the last decade, investigation of patients affected with PD has revealed that a large number of patients suffer from sporadic forms of PD, showing non-Mendelian inheritance pattern of the disease and lack of a clear family history with no clear distinction in clinical symptoms or pathological signs from familial forms (Kalinderi et al. 2016; Verstraeten et al. 2015). Early candidate gene studies have revealed that only a small percentage of the sporadic PD cases carry mutations in a number of previously known Mendelian PD genes including \( SNCA, \) \( PARKIN, \) \( LRRK2, \) and \( GBA1 \) (Table 1) (Maraganore et al. 2006; Satake et al. 2009; Zabetian et al. 2009). However, the etiology for a high proportion of sporadic PD cases remains largely unknown. It is assumed that the sporadic forms of PD are caused by the combined effects of common variations (polymorphisms with frequencies > 1%) in different genetic loci with minor to moderate effects on PD risk (average odds ratios (ORs) ~1.2) (Simon-Sanchez et al. 2009; Simón-Sánchez et al. 2011). In order to uncover the genetic architecture that impacts disease susceptibility in sporadic cases, more than 800 genome-wide association studies (GWAS) have been performed in the field of Parkinsonism during the last two decades, but most studies yielded inconsistent results. To alleviate this problem, GWAS meta-analysis has recently successfully been developed as a systematic approach to interpreting the genetic association findings of complex disease including neurodegenerative diseases (Consortium 2011; Evangelou et al. 2007). In addition, GWAS meta-analysis on 7,782,514 genetic variants in up to 13,708 PD cases and 95,282 controls from populations of European descent have been provided by a dedicated and freely available online database, PDGene (http://www.pdgene.org) (Lill et al. 2012). As illustrated in Table 2, twelve loci showed genome-wide significant association (ORs ≥ 1.1; \( p \) values < 5 × 10\(^{-8}\)) with PD risk from case–control genotype data in 4 or more independent samples: \( SNCA, \) \( TMEM175, \) \( STK39, \) \( TMEM229B, \) \( LRRK2, \) \( BCKDK, \) \( MIR4697, \) \( INPP5F, \) \( RIT2, \) \( GCH1, \) \( SIPA1L2, \) \( TMPRSS9 \) (Lill et al. 2012). However, despite this progress, the genetic etiology of PD, occurring in 40% of all cases remains unexplained by today (Consortium 2011).

**Discussion**

It is increasingly evident that Parkinson’s disease (PD) is a complex and progressive neurodegenerative disorder clinically characterized by a broad spectrum of motor and non-motor impairments. Over the past decades, both familial and sporadic forms of PD have been identified, with overlapping phenotypes. Family-based studies have successfully identified 23 loci or genes associated with PD. Subsequent functional characterization of the encoded proteins has revealed that lysosomal dysfunction, impaired mitophagy, deficiency of synaptic transmission, and vesicular recycling pathways can be considered as the key molecular mechanisms in spreading pathology of the disease that may be shared between familial and sporadic forms of PD. Accumulating evidence indicates that gene mutations lead to various abnormalities in one or several of these subcellular pathways and associate with neuronal loss in the substantia nigra pars compacta (SNc). Now, based on the pathological studies, degeneration of dopaminergic neurons in the SNc and subsequent reduction in the striatal concentration of dopamine are accepted as being responsible for spread of pathological features in both sporadic and familial PD (motor features of

| Gene       | Polymorphism | Location   | Alleles | Case–control samples | Meta OR | Meta P-value |
|------------|--------------|------------|---------|----------------------|---------|--------------|
| SNCA [− 19139 bp] | rs356182 | chr:90626111 | G versus A | 21 | 1.34 | 1.85e-82 |
| TMEM175    | rs34311866  | chr:951947  | C versus T | 21 | 1.26 | 6.00e-41 |
| STK39 [+ 24494 bp] | rs1955337 | chr:169129145 | T versus G | 21 | 1.21 | 1.67e-20 |
| TMEM229B   | rs1555399   | chr:67984370 | T versus A | 15 | 1.15 | 5.70e-16 |
| LRRK2      | rs76904798  | chr:1240614434 | T versus C | 21 | 1.16 | 4.86e-14 |
| BCKDK      | rs14235     | chr:31121793 | A versus G | 21 | 1.10 | 3.63e-12 |
| MIR4697 [− 3032 bp] | rs329648 | chr:133763567 | T versus C | 21 | 1.11 | 8.05e-12 |
| INPP5F     | rs117896735 | chr:121536327 | A versus G | 13 | 1.77 | 1.21e-11 |
| RIT2       | rs12456492  | chr:40673380 | G versus A | 21 | 1.10 | 2.15e-11 |
| GCH1       | rs7155501   | chr:55347827 | A versus G | 15 | 1.12 | 1.25e-10 |
| SIPA1L2    | rs10797576  | chr:232664611 | T versus C | 21 | 1.13 | 1.76e-10 |
| TMPRSS9 [− 26450 bp] | rs62120679 | chr:2363319 | T versus C | 13 | 1.14 | 2.52e-09 |
PD are mainly related to the dopamine deficit in the striatum, as dopamine plays a significant role in the control of motor function within brain) (Dickson et al. 2009). However, currently, there is no decisive description for why these disruptions affect dopaminergic neurons earlier and more profoundly than other neurons. One major common supposition for the selective vulnerability of SNc cells is the dopamine toxicity hypothesis. Dopamine metabolism is considered as a hot spot for the selective susceptibility of SNc cells to degeneration in PD (Segura-Aguilar et al. 2014). Dopamine metabolism produces highly reactive species and is vulnerable to different subcellular dysfunctions (Sulzer 2007). It is proposed that mitochondrial functional defects cause alterations in the mitochondrial respiratory chain as the main source of superoxide and hydrogen peroxide inside the neurons, and lead to the propagation of free radicals contributing to the oxidation of dopamine (Brieger et al. 2012). Also, deficiencies in the efficient elimination of damaged proteins or organelles (autophagy) due to impaired lysosome degradation pathway can lead to toxic protein aggregation and defective mitochondria accumulation inside the neuron which is associated with increased ROS formation as well as protein oxidation and enhanced vulnerability to oxidation of dopamine (Cook et al. 2012; Schapira et al. 2014). Moreover, it has been proven that reduced synaptic plasticity or impaired packaging of dopamine into the synaptic vesicles leads to an increased amount of cytosolic dopamine, which is readily susceptible to oxidation, and cause dopamine-mediated toxicity within the neurons (pH is lower inside the vesicles and dopamine cannot auto-oxidize) (Caudle et al. 2007; Zucca et al. 2014). Indeed, based on these observations, an emerging concept is that different gene mutations and subsequent mitochondrial dysfunctions, impaired lysosome degradation pathways, and reduced sequestration of dopamine into synaptic vesicles increase oxidative stress and interact with dopamine metabolism, which cause an exponential growth in the formation of highly reactive species of oxidized dopamine and precipitate lipid, protein, DNA, and other intracellular and membrane compounds oxidation as a critical step in the selective dopaminergic neuron death in the SNc over time (Jenner 2003; Segura-Aguilar et al. 2014).

In the past 30 years, this view that striatal dopamine loss secondary to degeneration of dopaminergic neurons might contribute to the pathogenesis of PD has guided the existing strategies for managing patients with PD and led to the development of dopamine replacement treatment using dopamine agonists (e.g., l-DOPA, ropinirole) and neuroprotective treatment (e.g., treatment with monoamine oxidase-B (MAO-B) inhibitors, glutamate antagonists, anti-apoptotic agents, growth factors) (Jenner 2004; Schapira 2009; Whone et al. 2003). Emerging evidence reveals that although dopaminergic treatment might provide some initial benefit in patients with PD, frequently lose antiparkinsonian efficacy, and develop levodopa-related motor complications and psychiatric manifestations, which means that many patients ultimately develop both motor and nonmotor problems (Parati et al. 1993; Schapira 2009). Recent knowledge offers cell replacement as a potential therapeutic opportunity for restoring striatal dopaminergic function in both familial and sporadic PD. It has been reported that Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) may serve as promising sources of cells for transplantation in the striatum of PD patients (Björklund et al. 2002; Cai et al. 2009; Takahashi and Yamanaka 2006). Despite the fact that cell replacement studies have provided evidence for restoring motor functions in animal models of PD, to date, cell therapy efforts in PD patients have failed to show substantial clinical improvement and in some cases were hampered by the development of graft-induced dyskinesias (Cai et al. 2009; Politis et al. 2011). In addition, there is a considerable risk that they can overgrow and form teratoma after transplantation (Brederlau et al. 2006). More recently, gene therapy based on the adeno-associated viral vector (AAV)-mediated delivery of neuroprotective agents to the basal ganglia nuclei has provided a possible alternative approach to the conventional pharmacological treatments. It is now known that these gene therapy-based approaches failed in improving the motor symptoms in clinical trials and doubts about its benefits compared with existing drug treatment (Gasmi et al. 2007; Kaplitt et al. 2007; Lim et al. 2010). However, beyond these obstacles, currently, there is a general agreement that continued success in identifying the new genes implicated in the pathogenesis of PD is the best possible way to figure out what goes wrong at the molecular level and to use this knowledge to designing etiologic treatments for this complex disorder. In fact, it is clearly hoped that greater understanding of the genetic basis in inherited PD coupled with advancements in viral-mediated gene delivery may lead to potential gene replacement therapies and genetic defect corrections within the basal ganglia (etiologic gene therapy approach) (Bünning et al. 2008; Singleton et al. 2013). In this context, several recent studies reported successful preclinical trials in multiple animal models based on the AAV-mediated delivery of PARKIN gene to the basal ganglia nuclei which reduced dopaminergic neurons degeneration and recovered motor functions (Manfredsson et al. 2007). Based on these findings, now, there is an incentive to broaden AAV-mediated gene replacement trials to other genetic defects associated with dopaminergic neuron degeneration, with this promising perspective that patients with different genetic defects may potentially benefit from gene replacement therapy in the future. Moreover, there is a common notion that understanding the potential mechanistic implications of these genes will broaden our options to design and produce...
efficient and specific drugs that appropriately intervene with the pathobiological process in both familial and sporadic PD (Singleton et al. 2013).

Additionally, with the advent of high-throughput genetic analysis techniques and the access to large patient samples, biomedical researches in the field of Parkinsonism have been radically changed. More recently, genome-wide association studies (GWASs) have been combined with meta-analysis and together have identified over 12 genetic risk factors. Ongoing researches demonstrated that these loci may be associated with increased risk for PD by affecting expression levels or splicing process of the biologically relevant transcripts (Consortium 2011; Simon-Sanchez et al. 2009). Currently, there is an assumption that identifying pathobiologically relevant transcripts within these risk loci and subsequently modulating their expression levels may provide novel potential therapeutic approaches for treating PD (Singleton et al. 2003). Also, aside from therapeutic interventions, it is worth mentioning that rapid progress in identifying the genes implicated either in the familial PD or in the sporadic PD as risk factors will be useful for diagnosing the disease in affected persons at an early stage and providing an opportunity to initiate appropriate therapeutic interventions at a presymptomatic stage in which a significant proportion of dopaminergic neurons are still alive and treatment is most likely to succeed. Moreover, considering the relationship between genetic variations within the risk loci and the level of gene expressions, it seems logical that genetic profiling of individuals affected with sporadic forms of the disease and also identifying the causative gene in patients affected with familial forms of the disease will be important in categorizing patients based on the pathogenicity mechanism and adopting appropriate treatment as well as the determining the drug dosage for treatments (Gibbs et al. 2010; Singleton et al. 2013).

Overall, given the genetically heterogeneous nature of the PD, elucidation of the genetic architecture of sporadic and familial PD improves diagnostic accuracy rates (sensitivity and specificity) and consequently enables presymptomatic diagnosis of the at-risk individuals as well as prenatal testing in the affected families. Moreover, it expands our knowledge of the disease genetic and neuropathologic mechanisms which can be of major importance for the development of disease-modifying therapeutic strategies. Ultimately, it enhances our ability to categorize various PD patients into genetic subtypes. This classification of patients based on the genetic etiology and underlying molecular mechanisms can pave the way for the efficient treatment of the patients through the effective intervention (slowing or halting) in the disease process.

Author Contributions AKM conceived the project, performed critical analysis of current topics, and wrote the manuscript. SC advised the conceptual ideas and provided critical feedback on the early draft. BB contributed to the final revision of the manuscript content. MRJ supervised the project and took the lead in overall direction and planning of the project. All authors discussed the results and contributed to the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.

References

Abou-Sleiman PM, Healy DG, Quinn N, Lees AJ, Wood NW (2003) The role of pathogenic DJ-1 mutations in Parkinson’s disease. Ann Neurol 54(3):283–286
Alcalay RN, Mejia-Santana H, Tang MX, Rosado L, Verbitsky M, Kissel et al (2009) Motor phenotype of LRRK2 G2019S carriers in early-onset Parkinson disease. Arch Neurol 66(12):1517–1522
Al-Din A, Wriekat A, Mubaidin A, Dasouki M, Hiart M (1994) Pallidopyramidal degeneration, supranuclear upgaze paresis and dementia: Kufor-Rakeb syndrome. Acta Neurol Scand 89(5):347–352
Ali IK, McKenzie L, Morley SJ, Jackson RJ (2001) Truncated initiation factor eIF4G lacking an eIF4E binding site can support capped mRNA translation. EMBO J 20(15):4233–4242
Al-Ramahi I, Pérez AM, Lim J, Zhang M, Sorensen R, De Haro M et al (2007) dAtaxin-2 mediates expanded Ataxin-1-induced neurodegeneration in a Drosophila model of SCA1. PLoS Genet 3(12):e234
Amnesi G, Savettieri G, Pugliese P, D’Amelio M, Tarantino P, Ragonese P et al (2005) DJ-1 mutations and parkinsonism-dementia-amytrophic lateral sclerosis complex. Ann Neurol 58(5):803–807
Appel-Cresswell S, Rajput AH, Sossi V, Thompson C, Silva V, Mckenzie J et al (2014) Clinical, positron emission tomography, and pathological studies of DNAJC13 p.N855S parkinsonism. Mov Disord 29:1684–1687
Arias S, Pak O, Sommer N, Finley JrR, Hüttetmann M, Weissmann N et al (2013) Oxygen-dependent expression of cytochrome c oxidase subunit 4–2 gene expression is mediated by transcription factors RBPJ, CXXC5 and CHCHD2. Nucleic Acids Res 41(4):2255–2266
Arias S, Bai M, Lee I, Springett R, Hüttetmann M, Grossman LI (2015) MNRR1 (formerly CHCHD2) is a bi-organellar regulator of mitochondrial metabolism. Mitochondrion 20:43–51
Balsinde J, Balboa MA (2005) Cellular regulation and proposed biological functions of group VIA calcium-independent phospholipase A 2 in activated cells. Cell Signal 17(9):1052–1062
Bandopadhyay R, Kingsbury AE, Cookson MR, Reid AR, Evans IM, Hope AD et al (2004) The expression of DJ-1 (PARK7) in normal human CNS and idiopathic Parkinson’s disease. Brain 127(2):420–430
Beck G, Shinzawa K, Hayakawa H, Baba K, Yasuda T, Sumi-Akamatu H et al (2015) Deficiency of calcium-independent phospholipase
A2 Beta induces brain iron accumulation through upregulation of divalent metal transporter 1. PLoS ONE 10(10):e0141629

Beck G, Shinzawa K, Hayakawa H, Baba K, Sumi-Akamaru H, Tsujimoto Y et al (2016) Progressive axonal degeneration of nigrostriatal dopaminergic neurons in calcium-independent phospholipase A2β knockout mice. PLoS ONE 11(4):e0153789

Berg D, Marek K, Ross GW, Poewe W (2012) Defining at-risk populations for Parkinson's disease: Lessons from ongoing studies. Mov Disord 27(5):656–665

Björklund LM, Sánchez-Pernaute R, Chung S, Andersson T, Chen IYC, McNaught KSP et al (2002) Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. Proc Natl Acad Sci USA 99(4):2344–2349

Bogaerts V, Nuytemans K, Reumers J, Pals P, Engelborghs S, Pickut B et al (2008) Genetic variability in the mitochondrial serine protease HTRA2 contributes to risk for Parkinson disease. Hum Mutat 29(6):832–840

Boldogh IR, Pon LA (2007) Mitochondria on the move. Trends Cell Biol 17(10):502–510

Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E et al (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. Science 299(5604):256–259

Bras J, Simón-Sánchez J, Federoff M, Morgadinho A, Januario C, Ribeiro M et al (2008) Lack of replication of association between GIGYF2 variants and Parkinson disease. Hum Mol Genet 18(2):341–346

Brederlau A, Correia AS, Anisimov SV, Elmi M, Paul G, Roybon C, Bandyopadhyay S et al (2004) The Parkinson's disease-linked proteins Fbxo7 and Parkin interact to mediate mitophagy. BBA-Mol Cell Res 1843(7):1295–1307

Clemente CM, McNally RS, Conedera S, Apaydin H, Li Y, Yoshino H, Ikeda A, Matsushima T et al (2012) Subcellular localization of recombinant mitofusins in human embryonic stem cell-derived cells to a rat model of Parkinson's disease: effect of in vitro differentiation on glial survival and teratoma formation. Stem Cells 24(6):1433–1440

Crijns A, Schiavone S, Miller FJ Jr, Krause KH (2012) Reactive oxygen species: from health to disease. Swiss Med Wkly 142:w13659

Bugarcic A, Zhe Y, Kerr MC, Griffin J, Collins BM, Teasdale RD (2011) Vps26A and Vps26B subunits define distinct retromer complexes. Traffic 12(12):1759–1773

Büning H, Perabo L, Coutelle O, Quadt-Humme S, Hallek M (2008) Mitochondria on the move. Trends Cell Biol 18(10):496–502

Cilenti L, Ambivero CT, Ward N, Alnemri ES, Germain D, Zervos AS (2014) Inactivation of Omi/HtrA2 protease leads to the deregulation of mitochondrial Mulan E3 ubiquitin ligase and increased mitophagy. BBA-Mol Cell Res 1843(7):1295–1307

Clemens CM, McNally RS, Conedera S, Apaydin H, Li Y, Yoshino H, Ikeda A, Matsushima T et al (2012) Oxidative damage of DJ-1 is linked to sporadic Parkinson and Alzheimer diseases. J Biol Chem 281(16):10816–10824

Choy RWY, Cheng Z, Schekman R (2012) Amyloid precursor protein (APP) traffics from the cell surface via endosomes for amyloid β (Aβ) production in the trans-Golgi network. Proc Natl Acad Sci USA 109(30):E2077–E2082

Crosiers D, Ceulemans B, Meeus B, Nuytemans K, Pals P, Van Broeckhoven C, Ribeiro M et al (2008) Lack of replication of association between GIGYF2 variants and Parkinson disease. Hum Mol Genet 18(2):341–346

Damiano M, Gautier CA, Quadt-Humme S, Elmi M, Paul G, Roybon C et al (2012) Defining at-risk populations for Parkinson’s disease: Lessons from ongoing studies. Mov Disord 27(5):656–665

DeStefano AL, Lew MF, Golbe LI, Mark MH, Lazzarini AM, Guttman et al (2002) PARK3 influences age at onset in Parkinson...
Gasmì M, Brandon EP, Herzog CD, Wilson A, Bishop KM, Hofer EK et al (2007) AAV2-mediated delivery of human neurutrin to the rat nigrostriatal system: long-term efficacy and tolerability of CERE-120 for Parkinson’s disease. Neurobiol Dis 27(1):67–76

Gautier CA, Kitada T, Shen J (2008) Loss of PINK1 causes mitochondrial functional defects and increased sensitivity to oxidative stress. Proc Natl Acad Sci USA 105(32):11364–11369

Gegh ME, Cooper JM, Chau KY, Rojo M, Schapira AH, Taanman JW (2010) Mitoﬁnus 1 and mitofusin 2 are ubiquitinated in a PINK1/ parkin-dependent manner upon induction of mitophagy. Hum Mol Genet 19(24):4861–4870

Geisler S, Holmström KM, Skujat D, Fiesel FC, Rothfuss OC, Kahle PJ et al (2010) PINK1/Parkin-mediated mitophagy is dependent on VDAC1 and p62/SQSTM1. Nat Cell Biol 12(2):119–131

Gibbs JR, van der Brug MP, Hernandez DG, Traylor BJ, Nalls MA, Lai SL et al (2010) Abundant quantitative trait loci exist for DNA methylation and gene expression in human brain. PLoS Genet 6(5):e1000952

Gilks WP, Abou-Sleiman PM, Gandhi S, Jain S, Singleton A, Lees AJ et al (2005) A common LRRK2 mutation in idiopathic Parkinson’s disease. Lancet 365(9457):415–416

Giovannone B, Lee E, Laviola L, Giorgio F, Cleveland KA, Smith RJ (2003) Two novel proteins that are linked to insulin-like growth factor (IGF-I) receptors by the Grb10 adapter and modulate IGF-I signaling. J Biol Chem 278(34):31564–31573

Giovannone B, Tsiaras WG, de la Monte S, Klysik J, Lautier C, Karashchuk G et al (2009) Gigyf2 gene disruption in mice results in neurodegeneration and altered insulin-like growth factor signaling. Hum Mol Genet 18(23):4629–4639

Güler AD, Chesi A, Geddie ML, Strathern KE, Hamamichi S, Hill KJ et al (2009) α-Synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity. Nat Genet 41(3):308–315

Goker-Alpan O, Schiﬀmann R, LaMarca M, Nussbaum R, Mcinerney-Leo A, Sidransky E (2004) Parkinsonism among Gaucher disease carriers. J Med Genet 41(12):937–940

Grabowski GA (2008) Phenotype, diagnosis, and treatment of Gaucher’s disease. Lancet 372(9645):1263–1271

Greene AW, Grenier K, Aguileta MA, Muiпе S, Farzifard R, Haque ME et al (2012) Mitochondrial processing peptidase regulates PINK1 processing, import and Parkin recruitment. EMBO Rep 13(4):378–385

Grünewald A, Arns B, Seibler P, Rakovic A, Münchau A, Ramirez A et al (2012) ATP13A2 mutations impair mitochondrial function in fibroblasts from patients with Kufor-Rakeb syndrome. Neurobiol Aging 33(8):e1841-e1847

Guirarte TR (2010) Manganese and Parkinson’s disease: a critical review and new ﬁndings. Environ Health Perspect 118(8):1071

Guo Y, Jankovic J, Zhu S, Le W, Song Z, Xie W et al (2009) GIGYF2 is critical for DJ-1 to repress p53 transcriptional activity. J Biol Chem 283(7):4022–4030

Fan J, Ren H, Fei E, Jia N, Ying Z, Jiang P et al (2008b) Sumoylation is critical for DJ-1 to repress p53 transcriptional activity. FEBS Lett 582(7):1151–1156

Follett J, Norwood SJ, Hamilton NA, Mohan M, Kovtun O, Tay S et al (2014) ATP13A2 mutations impair mitochondrial function: where are we at? Neuroscientist 20(2):230–244

Franco-Iborra S, Vila M, Perier C (2016) The Parkinson disease mitochondrial hypothesis: where are we at? Neuroscientist 22(3):266–277

Frederick RL, Shaw JM (2007) Moving mitochondria: establishing distribution of an essential organelle. Traffic 8(12):1668–1675

Frederick RL, Shaw JM (2007) Moving mitochondria: establishing distribution of an essential organelle. Traffic 8(12):1668–1675

Fukushima T, Tan X, Luo Y, Kanda H (2011) Serum vitamins and mitochondrial function: a genome-wide linkage and sequencing study. Lancet Neurol 10(6):631–641

Di Fazio A, Fabrizio E, Thomas A, Marconi R, Tinazzi M et al (2009b) Gigyf2 mutations are not a frequent cause of familial Parkinson’s disease. Parkinsonism Relat Disord 15(9):703–705

Dickson DB, Braakh H, Duda JE, Ducyacert A, Gasser T, Halliday GM et al (2009) Neuropathological assessment of Parkinson’s disease: refining the diagnostic criteria. Lancet Neurol 8(12):1150–1157

Dufresne AM, Smith RJ (2005) The adapter protein Grb10 is an essential, early-onset parkinsonian-tyramide syndrome. Neurology 72(3):240–245

Dunbarne SA, Nissley S, Furlanetto R (1996) Evi-1172 Cellular and Molecular Neurobiology (2018) 38:1153–1178

Dey B, Frick K, Lopacynski W, Nissley S, Furlanetto R (1996) Evidence for the direct interaction of the insulin-like growth factor I receptor with IRS-1, Shc, and Grb10. Mol Endocrinol 10(6):631–641

Di Fazio A, Rohé CF, Ferreira J, Chien HF, Vacca L, Stocchi F et al (2005) A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson’s disease. Lancet 365(9457):412–415

Di Fazio A, Dekker M, Montagna P, Baruzzi A, Yonova E, Guedes LC et al (2009a) FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology 72(3):240–245

Di Fazio A, Furuya N, Vacca L, Stocchi F et al (2005) A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson’s disease. Lancet 365(9457):412–415

Di Fazio A, Dekker M, Montagna P, Baruzzi A, Yonova E, Guedes LC et al (2009a) FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology 72(3):240–245

Di Fazio A, Rohé CF, Ferreira J, Chien HF, Vacca L, Stocchi F et al (2005) A frequent LRRK2 gene mutation associated with autosomal dominant Parkinson’s disease. Lancet 365(9457):412–415

Di Fazio A, Dekker M, Montagna P, Baruzzi A, Yonova E, Guedes LC et al (2009a) FBXO7 mutations cause autosomal recessive, early-onset parkinsonian-pyramidal syndrome. Neurology 72(3):240–245

Di Fazio A, Fabrizio E, Thomas A, Marconi R, Tinazzi M et al (2009b) Gigyf2 mutations are not a frequent cause of familial Parkinson’s disease. Parkinsonism Relat Disord 15(9):703–705
Hansen H, Svensson U, Zhu J, Laviola L, Giorgino F, Wolf G et al (1996) Interaction between the Grb10 SH2 domain and the insulin receptor carboxyl terminus. J Biol Chem 271(15):8882–8886

Hardy J, Lewis P, Revesz T, Lees A, Paisan-Ruiz C (2009) The genetics of Parkinson’s disease: a critical review. Curr Opin Genet Dev 19(3):254–265

Healy DG, Abou-Sleiman PM, Wood NW (2004) Genetic causes of Parkinson’s disease: UCH-L1. Cell Tissue Res 318(1):189–194

Healy DG, Falchi M, O’Sullivan SS, Bonifati V, Durr A, Bressman S et al (2008) Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson’s disease: a case-control study. Lancet Neurol 7(7):583–590

Heo JM, Ordureau A, Paulo JA, Rinehart J, Harper JW (2015) The PINK1-PARKIN mitochondrial ubiquitylation pathway drives a program of OPTN/ND5P2 recruitment and TBK1 activation to promote mitophagy. Mol Cell 60(1):7–20

Hernandez DG, Reed X, Singleton AB (2016) Genetics in Parkinson disease: Mendelian versus non-Mendelian inheritance. J Neurochem 139(S1):59–74

Hicks AA, Petrussson H, Jonsson T, Stefansson H, Johannsdottir HS, Sainz J et al (2002) A susceptibility gene for late-onset idiopathic Parkinson’s disease. Ann Neurol 52(5):549–555

Higashi S, Iseki E, Minegishi M, Togo T, Kabuta T, Wada K (2010) GIGYF2 is present in endosomal compartments in the mammalian brains and enhances IGFl-induced ERK1/2 activation. J Neurochem 115(2):423–437

Hofseth LJ, Hussain SP, Harris CC (2004) p53: 25 years after its discovery. Trends Pharmacol Sci 25(4):177–181

Ishikawa S, Taira T, Takahashi-Niki K, Niki T, Ariga H, Iguchi-Ariga SM (2012) Stimulation of vesicular monoamine transporter 2 activity by DJ-1 in SH-SY5Y cells. Biochem Biophys Res Commun 421(4):813–818

Itoh K, Nakamura K, Iijima M, Sasaki H (2013) Mitochondrial dynamics in neurodegeneration. Trends Cell Biol 23(2):64–71

Jankovic J (2008) Parkinson’s disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatr 79(4):368–376

Jenner P (2004) Preclinical evidence for neuroprotection with monoamine oxidase-B inhibitors in Parkinson’s disease. Neurology 63(7 suppl 2):S13–S22

Jiménez-Jiménez FJ, Fernández-Calle P, Martínez-Vanaclocha M, Herrero E, Molina JA, Vázquez A et al (1992) Serum levels of zinc and copper in patients with Parkinson’s disease. J Neurol Sci 112(1):30–33

Jin SM, Lazaro M, Wang C, Kane LA, Narendran DP, Youle RJ (2010) Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. J Cell Biol 191(5):933–942

Jones JM, Datta P, Srinivasula SM, Ji W, Gupta S, Zhang Z et al (2003) Loss of Omi mitochondrial protease activity causes the neuromuscular disorder of mnd2 mutant mice. Nature 425(6959):721–727

Junn E, Jang WH, Zhao X, Jeong BS, Mouradian MM (2009) Mitochondrial localization of DJ-1 leads to enhanced neuroprotection. J Neurosci Res 87(1):123–129

Kabeya Y, Mizushima N, Yamamoto A, Ohshimi-Oakamoto S, Ohsumi Y, Yoshimori T (2004) LC3, GABARAP and GATE16 localize to autophagosomal membrane depending on form-II formation. J Cell Sci 117(13):2805–2812

Kalinderi K, Bostantjopoulou S, Fidani L (2016) The genetic background of Parkinson’s disease: current progress and future prospects. Acta Neurol Scand 134(5):314–326

Kane LA, Lazaro M, Fogel AI, Li Y, Yamano K, Sarraf SA et al (2014) PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J Cell Biol 201:402104

Kang S, Louboutin J, Datta P, Landel C, Martinet D, Zervos A et al (2013) Loss of HtrA2/Omi activity in non-neuronal tissues of adult mice causes premature aging. Cell Death Differ 20(2):259–269

Kaplitt MG, Feigin A, Tang C, Fitzsimons HL, Mattis P, Lawlor PA et al (2007) Safety and tolerability of gene therapy with an adeno-associated virus (AAV) borne GAD gene for Parkinson’s disease: an open-label, phase I trial. Lancet 369(9579):2097–2105

Kato I, Maita H, Takahashi-Niki K, Saito Y, Naguchi N, Iguchi-Ariga SM et al (2013) Oxidized DJ-1 inhibits p53 by sequestering p53 from promoters in a DNA-binding affinity-dependent manner. Mol Cell Biol 33(2):340–359

Kauther KM, Höft C, Rissling I, Oertel WH, Müller JC (2011) The PLA2G6 gene in early-onset Parkinson’s disease. Mov Disord 26(13):2415–2417

Kazlauskaite A, Kondapalli C, Gourlay R, Campbell DG, Ritorto MS, Hofmann K et al (2014) Parkin is activated by PINK1-dependent phosphorylation of ubiquitin at Ser65. Biochem J 460(1):127–141

Keller MF, Saad M, Bras J, Bettella F, Nicolauo N, Simón-Sánchez J et al (2012) Using genome-wide complex trait analysis to quantify ‘missing heritability’ in Parkinson’s disease. Hum Mol Genet 21(22):4996–5009

Kempster PA, Hurwitz B, Lees AJ (2007) A new look at James Parkinson’s essay on the shaking palsy. Neurology 69(5):482–485

Kessler TW, Wakabayashi N, Biswal S (2007) Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. Annu Rev Pharmacol Toxicol 47:89–116

Kieper N, Holmström KM, Ciceri D, Fiesel FC, Wolburg H, Ziviani E et al (2010) Modulation of mitochondrial function and morphology by interaction of Omi/HtrA2 with the mitochondrial fusion factor OPA1. Exp Cell Res 316(7):1213–1224

Kim SJ, Park YJ, Hwang IY, Youdim MB, Park KS, Oh YJ (2012) Nuclear translocation of DJ-1 during oxidative stress-induced neuronal cell death. Free Radic Biol Med 53(4):936–950

Kinumi T, Jimata J, Taira T, Ariga H, Niki E (2004) Cysteine-106 of DJ-1 is the most sensitive cysteine residue to hydrogen peroxide-mediated oxidation in vivo in human umbilical vein endothelial cells. Biochem Biophys Res Commun 317(3):722–728
Klein C, Hedrich K, Wellenbrock C, Kann M, Harris J, Marder K et al (2003) Frequency of parkin mutations in late-onset Parkinson’s disease. Ann Neurol 54(3):415–416

Kojovic M, Sheerin UM, Rubio-Agustí I, Saha A, Bras J, Gibbons V et al (2012) Young-onset parkinsonism due to homozygous duplication of α-synuclein in a consanguineous family. Mov Disord 27(14):1829–1830

Kondapalli C, Kazlauskaite A, Zhang N, Woodroof HI, Campbell Klein C, Hedrich K, Wellenbrock C, Kann M, Harris J, Marder K et al (2012) PINK1 is activated by mitochondrial membrane potential depolarization and stimulates Parkin E3 ligase activity by phosphorylating Serine 65. Open Biol 2(5):120080

Kong SM, Chan BK, Park JS, Hill KJ, Atken JB, Cottle L et al (2014) Parkinson’s disease-linked human PARK9/ATP13A2 maintains zinc homeostasis and promotes α-Synuclein externalization via exosomes. Hum Mol Genet 23(11):2816–2833

Kono S, Shirakawa K, Ouchi Y, Sakamoto M, Ida H, Sugiura T et al (2003) Frequency of parkin mutations in late-onset Parkinson’s disease. Arch Neurol 60(10):1360–1364

Koroglu C, Baysal L, Cetinkaya M, Karasoy H, Tolun A (2013) Mutations in the GIGYF2 (TNRC15) gene at the 13q22.2 locus cause infantile neurodegeneration and 3-methylglutaconic aciduria. J Med Genet 50(6):391–393

Krebs CE, Karkheiran S, Powell JC, Cao M, Makarov V, Darvish H et al (2013) The Sac1 domain of SYNJ1 identified mutated in a family with early-onset progressive parkinsonism with generalized seizures. Hum Mutat 34:1200–1207

Krüger L, Daly MJ, Reeye-Daly MP, Lander ES (1996) Parametric and nonparametric linkage analysis: a unified multipoint approach. Am J Hum Genet 58(6):1347

Kumar KR, Weissenbach A, Heldmann M, Kasten M, Tunc S, Sue CM et al (2012) Frequency of the D620N mutation in VPS35 in Parkinson disease. Arch Neurol 69(10):1360–1364

Lander E, Krüger L (1995) Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat Genet 11(3):241–247

Langliai P, Dong LQ, Ramos FJ, Hu D, Li Y, Quon MJ et al (2004) Negative regulation of insulin-stimulated mitogen-activated protein kinase signaling by Gβ10. Mol Endocrinol 18(2):350–358

Laurent-Mathia V, Deroç D, Prébois C, Katunuma N, Liaudet-Coopman E (2006) Processing of human cathepsin D is independent to genetic susceptibility factors. Hum Mol Genet 11(3):241–247

Lautier C, Goldwurm S, Dürr A, Giovannone B, Tsiaras WG, Pezzoli G et al (2008) Mutations in the GIGYF2 (TNRC15) gene at the PARK1 locus in familial Parkinson disease. Am J Hum Genet 82(4):822–833

Lazarou M, Jin SM, Kane LA, Youle RJ (2012) Role of PINK1 binding to the TOM complex and alternate intracellular membranes in recruitment and activation of the E3 ligase Parkin. Dev Cell 22(2):320–333

Leroy E, Boyer R, Auburger G, Leube B, ULM G, Mezey E et al (1998) The ubiquitin pathway in Parkinson’s disease. Nature 395(6701):451–452

Lesage S, Brice A (2009) Parkinson’s disease: from monogenic forms to genetic susceptibility factors. Hum Mol Genet 18(1):48–59

Lesage S, Anheim M, Letournel F, Bousset L, Honoré A, Rozas N et al (2013) G51D α-synuclein mutation causes a novel Parkinsonian-pyramidal syndrome. Ann Neurol 73(4):459–471

Lesage S, Drouet V, Majounie E, Deramecourt V, Jacoupuy 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(3):500–513

Lill CM, Roehr JT, McQueen MB, Kavvoura FK, Bagade S, Schjeide BMM et al (2012) Comprehensive research synopsis and systematic meta-analyses in Parkinson’s disease genetics: the PDGene database. PLoS Genet 8(3):e1002548

Lim ST, Airavaara M, Harvey BK (2010) Viral vectors for neurotrophic factor delivery: a gene therapy approach for neurodegenerative diseases of the CNS. Pharmacol Res 61(1):14–26

Lin MK, Farrer MJ (2014) Genetics and genomics of Parkinson’s disease. Genome Med 6(6):48

Lin L, Ozaki T, Takada Y, Kageyama Y, Nakamura Y, Hata A et al (2005) Topors, a p53 and topoisomerase I-binding RING finger protein, is a coactivator of p53 in growth suppression induced by DNA damage. Oncogene 24(21):3385–3396

Lin CH, Chen ML, Chen GS, Tai CH, Wu RM (2011) Novel variant Pro143Ala in HTRA2 contributes to Parkinson’s disease by inducing hyperphosphorylation of HTRA2 protein in mitochondria. Hum Genet 130(6):817–827

Liu S, Ninan I, Antonova I, Battaglia F, Trinchese F, Narasanna A et al (2004) α-Synuclein produces a long-lasting increase in neurotransmitter release. EMBO J 23(22):4506–4516

Liu S, Sawada T, Lee S, Yu W, Silverio G, Alapat P et al (2012a) Parkinson’s disease-associated kinase PINK1 regulates Miro protein level and axonal transport of mitochondria. PLoS Genet 8(3):e1002537

Liu L, Feng D, Chen G, Chen M, Zheng Q, Song P et al (2012b) Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat Cell Biol 14(2):177–185

Liu Y, Clegg H, Leslie P, Di J, Tollini L, He Y et al (2015) CHCHD2 inhibits apoptosis by interacting with Bcl-x L to regulate Bax activation. Cell Death Differ 22(6):1035

Lohmann E, Periquet M, Bonifati V, Wood NW, De Michele G, Bonnet AM et al (2003) How much phenotypic variation can be attributed to parkin genotype? Ann Neurol 54(2):176–185

Lohmann E, Thobois S, Lesage S, Broussolle E, du Montcel ST, Ribeiro MJ et al (2009) A multidisciplinary study of patients with early-onset PD with and without parkin mutations. Neurology 72(2):110–116

Lotharius J, Brundin P (2002) Impaired dopamine storage resulting from α-synuclein mutations may contribute to the pathogenesis of Parkinson’s disease. Hum Mol Genet 11(20):2395–2407

Lu CS, Chou YHW, Kuo PC, Chang HC, Weng YH (2004) The parkinson-competitive function of spinocerebellar ataxia type 2. Arch Neurol 61(1):35–38

Lücking CB, Dürr A, Bonifati V, Vaughan J, De Michele G, Gasser T et al (2000) Association between early-onset Parkinson’s disease and mutations in the parkin gene. N Engl J Med 342(21):1560–1567

Mandel H, Saita S, Edvardsson S, Jalas C, Shaag A, Goldsher D et al (2016) Deficiency of HTRA2/Omi is associated with infantile neurodegeneration and 3-methylglutaconic aciduria. J Med Genet. https://doi.org/10.1136/jmedgenet-2016-103922

Manfredsson FP, Burger C, Sullivan LF, Muzyczka N, Lewin AS, Mandel RJ (2007) rAAV-mediated nigral human parkin over-expression partially ameliorates motor deficits via enhanced dopamine neurotransmission in a rat model of Parkinson’s disease. Exp Neurol 207(2):289–301

Maraganore DM, De Andrade M, Elbaz A, Farrer MJ, Ioannidis JP, Krüger R et al (2006) Collaborative analysis of α-synuclein gene promoter variability and Parkinson disease. JAMA 296(6):661–670
Narendra DP, Walker JE, Youle R (2012) Mitochondrial quality control mediated by PINK1 and Parkin: links to parkinsonism. Cold Spring Harb Perspect Biol 4(11):a011338

Nelson DE, Randle SJ, Laman H (2013) Beyond ubiquitination: the atypical functions of Fbxo7 and other F-box proteins. Open Biol 3(10):130131

Nemani VM, Lu W, Berge V, Nakamura K, Onoa B, Lee MK et al (2010) Increased expression of α-synuclein reduces neurotransmitter release by inhibiting synaptic vesicle reclustering after endocytosis. Neuron 65(1):66–79

Nicholls WC, Pankratz N, Hernandez D, Paisán-Ruiz C, Jain S, Halter CA et al (2005) Genetic screening for a single common LRRK2 mutation in familial Parkinson’s disease. Lancet 365(9457):410–412

Nishikawa K, Li H, Kawamura R, Osaka H, Wang YL, Hara Y et al (2003) Alterations of structure and hydroxyl activity of parkinsonism-associated human ubiquitin carboxyl-terminal hydroxyl L1 variants. Biochem biophys Res Commun 304(1):176–182

Nikiliza A, Mutez E, Simonin C, Lepître F, Duflot A, Figéac M et al (2016) RNA-binding disturbances as a continuum from spinocerebellar ataxia type 2 to Parkinson disease. Neurobiol Dis 96:312–322

Nowak DM, Pitarque JA, Molinari A, Bejjani BA, Gajec M (2012) Linkage analysis as an approach for disease-related loci identification. Comput Methods Sci Technol 18:95–101

Nuytemans K, Thuesen J, Cruts M, Van Broeckhoven C (2010) Genetic etiology of Parkinson disease associated with mutations in the SNCA, PARK2, PINK1, PARK7, and LRRK2 genes: a mutation update. Hum Mutat 31(7):763–780

O’sullivan SS, Williams DR, Gallagher DA, Massey LA, Silvera-Moriyama L, Lees AJ (2008) Nonmotor symptoms as presenting complaints in Parkinson’s disease: a clinicopathological study. Mov Disord 23(1):101–106

Okatsu K, Uno M, Koyano F, Go E, Kimura M, Oka T et al (2013) A dimeric PINK1-containing complex on depolarized mitochondria stimulates Parkin recruitment. J Biol Chem 288(51):36372–36384

Oláhová M, Thompson K, Hardy SA, Barbosa IA, Besse A, Anagnostou ME et al (2017) Pathogenic variants in HTRA2 cause an early-onset mitochondrial syndrome associated with 3-methylglutaconic aciduria. J Inherit Metab Dis 40(1):121

Ogliati S, DE Rosa A, Quadri M, Criscuolo C, Breedveld GJ, Picillo M et al (2014) PARK20 caused by SYNJ1 homozygous Arg258Gln mutation in a new Italian family. Neurogenetics 15:183–188

Ogliati S, Quadri M, Fang MY, Rood J, Saute JA, Chien HF et al (2016) DAIJC6 mutations associated with early-onset Parkinson’s disease. Ann Neurol 79:244–256

Osaka H, Wang YL, Takada K, Takizawa S, Setsuei R, Li H et al (2003) Ubiquitin carboxy-terminal hydroxyl L1 binds to and stabilizes monoubiquitin in neuron. Hum Mol Genet 12(16):2039–2049

Otsu K, Murakawa T, Yamaguchi O (2015) BCL2L13 is a mammalian homolog of the yeast mitophagy receptor Atg32. Autophagy 11(10):1932–1933

Ott J, Wang J, Leal SM (2015) Genetic linkage analysis in the age of whole-genome sequencing. Nat Rev Genet 16(5):275–284

Ottolini D, Cali T, Negro A, Brini M (2013) The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. Hum Mol Genet 22(11):2152–2163

Paisan-Ruiz C, Bhatia KP, Li A, Hernandez D, Davis M, Wood NW et al (2009) Characterization of PLA2G6 as a locus for dystonia-parkinsonism. Ann Neurol 65(1):19–23

Paisán-Ruiz C, Guevara R, Federoff H, Hanagasi H, Sina F, Elahi E et al (2010) Early-onset L-dopa-responsive parkinsonism with
pyramidal signs due to ATP13A2, PLA2G6, FBXO7 and spatac- 
sin mutations. Mov Disord 25(12):1791–1800
Pals P, Van Everbroeck B, Grubben B, Kristina Viana M, Dom R, van 
der Linden C et al (2003) Case–control study of environmental 
risk factors for Parkinson’s disease in Belgium. Eur J Epidemiol 
18(12):1133–1142
Pankratz N, Nichols WC, Uniacke SK, Halter C, Rudolph A, Shults C 
et al (2002) Genome screen to identify susceptibility genes for 
Parkinson disease in a sample without parkin mutations. Am J 
Hum Genet 71(1):124–135
Pankratz N, Nichols WC, Uniacke SK, Halter C, Murrell J, Rudolph 
A et al (2003) Genome-wide linkage analysis and evidence of 
gene-by-gene interactions in a sample of 362 multiplex Parkinson 
disease families. Hum Mol Genet 12(20):2599–2608
Pao KC, Stanley M, Han C, Lai YC, Murphy P, Balk K et al (2016) 
Probes of ubiquitin E3 ligases enable systematic dissection of 
parkin activation. Nat Chem Biol 12(5):324–331
Parati E, Fetoni V, Geminiani G, Soliveri P, Giovanni G, Testa D 
et al (1993) Response to L-DOPA in multiple system atrophy. 
Clin Neuropharmacol 16(2):139–144
Park J, Lee SB, Lee S, Kim Y, Song S, Kim S et al (2006) Mitochon-
drial dysfunction in Drosophila PINK1 mutants is comple-
timented by parkin. Nat Reviews 41(7097):1157–1161
Payami H, Nutt J, Gancher S, Bird T, McNeal MG, Seltzer WK et al 
(2003) SCOA2 may present as levodopa-responsive parkinson-
ism. Mov Disord 18(4):425–429
Periquet M, Latouche M, Lohmann E, Rawal N, De Michele 
G, Ricard S et al (2003) Parkin mutations are frequent in 
patients with isolated early-onset parkinsonism. Brain 
126(6):1271–1278
Petrucli L, O'Farrell C, Lockhart PJ, Baptista M, Kehoe K, Vink L 
et al (2002) Parkin protects against the toxicity associated with 
mutant α-synuclein: proteasome dysfunction selectively affects 
catecholaminergic neurons. Neurom 36(6):1007–1019
Pickrell AM, Youle RJ (2015) The roles of PINK1, parkin, and mito-
chondrial fusion-promoting factor mitofusin is a substrate of the 
mitochondrial fidelity in Parkinson’s disease. Neuron 85(2):257–273
Pals P, Van Everbroeck B, Grubben B, Kristina Viana M, Dom R, van 
der Linden C et al (2003) Case–control study of environmental 
risk factors for Parkinson’s disease in Belgium. Eur J Epidemiol 
18(12):1133–1142
Randle J, Laman S H (2017) Structure and function of Fbxo7/PARK15 
in Parkinson’s disease. Curr Protein Pept Sci 18(7):715–724
Rathke-Hartlieb S, Scholmann U, Heimann P, Meissler MH, Jockusch 
H, Bartsch JW (2002) Progressive loss of striatal neurons causes 
motor dysfunction in MND2 mutant mice and is not prevented 
by Bcl-2. Exp Neurol 175(1):87–97
Rentschler G, Covolo L, Haddad AA, Lucchini RG, Zoni S, Broberg 
K (2012) ATP13A2 (PARK9) polymorphisms influence the neu-
rotoxic effects of manganese. Neurotoxicology 33(4):697–702
Ross JP, Dupre N, Daunviellies Y, Strong S, Ambalavanan A, Spiegel-
man D et al (2016) Analysis of DNAJC13 mutations in French-
Canadian/French cohort of Parkinson’s disease. Neurobiol Aging 
45:e13–e17
Ryan BJ, Hoek S, Fon EA, Wade-Martins R (2015) Mitochondrial dys-
function and mitophagy in Parkinson’s: from familial to sporadic 
disease. Trends Biochem Sci 40(4):200–210
Saez-Atienez S, Bonet-Ponce L, Blesa J, Romero F, Murphy M, Jor-
dan J et al (2014) The LRRK2 inhibitor GSK257821A induces protective autophagy in SH-SY5Y cells: involvement of Drp-
1-mediated mitochondrial fission and mitochondrial-derived 
ROS signaling. Cell Death Dis 5(8):e1368
Saigo H, Wang YL, Suh JG, Yamashiki T, Sakai Y, Kiyosawa H et al 
(1999) Intragenic deletion in the gene encoding ubiquitin 
carbonyl-terminal hydrolase in gud mice. Nat Genet 23(1):47–51
Sarraf SA, Raman M, Guarani-Pereira V, Sowa ME, Huttlin EL, Gygi 
SP et al (2013) Landscape of the PARKIN-dependent ubiqui-
tylyse in response to mitochondrial depolarization. Nature 
496(7445):372–376
Satake W, Nakabayashi Y, Mizuta I, Hirota Y, Ita C, Kubo M et al 
(2009) Genome-wide association study identifies common vari-
ants at four loci as genetic risk factors for Parkinson’s disease. 
Nat Genet 41(12):1303–1307
Satterfield TF, Pallancj LJ (2006) Axatin-2 and its Drosophila homolog, ATX2, physically assemble with polyribosomes. Hum 
Mol Genet 15(16):2523–2532
Scaparla AH (2009) Neurobiology and treatment of Parkinson’s dis-
case. Trend Pharmacol Sci 30(1):41–47
Scaparla AH, Jenner P (2011) Etiology and pathogenesis of Parkinson’s 
disease. Mov Disord 26(6):1049–1055
Scaparla AH, Olanow CW, Greenamyre JT, Bezd E (2014) Slow-
ing of neurodegeneration in Parkinson’s disease and Hun-
tington’s disease: future therapeutic perspectives. Lancet 
384(9942):545–555
Schneider RJ, Sonenberg N (2007) Translational control in cancer 
development and progression. Cold Spring Harbor Monogr Ser 
48:401
Schrag A, Ben-Shlomo Y, Quinn N (2000) Cross sectional prevalence 
survey of idiopathic Parkinson’s disease and parkinsonism in 
London. BMJ 321(7252):21–22
Schreglmann SR, Houlden H (2016) VPS13C—another hint at mito-
chondrial dysfunction in familial Parkinson’s disease. Mov Dis-
ord 31(9):1340–1340
Seaman MN (2007) Identification of a novel conserved sorting motif 
required for retromer-mediated endosome-to-TGN retrieval. J 
Cell Sci 120(14):2378–2389
Segura-Aguilar J, Paris I, Muñoz P, Ferrari E, Zecca L, Zucca FA 
(2014) Protective and toxic roles of dopamine in Parkinson’s 
disease. J Neurochem 129(6):898–915
Shen Q, Yamano K, Head BP, Kawajiri S, Cheung JT, Wang C et al 
(2014) Mutations in FIS1 disrupt orderly disposal of defective mitochondria. Mol Biol Cell 25(1):145–159
Shimura H, Hattori N, Kubo SI, Mizuno Y, Asakawa S, Minoshima S 
et al (2000) Familial Parkinson disease gene product, parkin, is a 
ubiquitin-protein ligase. Nat Genet 25(3):302–305
Springer
Shinzawa K, Sumi H, Ikawa M, Matsuoka Y, Okabe M, Sakoda S et al (2008) Neuroaxonal dystrophy caused by group VIA phospholipase A2 deficiency in mice: a model of human neurodegenerative disease. J Neurosci 28(9):2212–2220

Shiura H, Miyoshi N, Konishi A, Wakisaka-Saito N, Suzuki R, Muguruma K et al (2005) Meg1/Grb10 overexpression causes postnatal growth retardation and insulin resistance via negative modulation of the IGF1R and IR cascades. Biochem Biophys Res Commun 329(3):909–916

Shojaei S, Sina F, Banihosseini SS, Kazemi MH, Kalhor R, Shahidi Shiura H, Miyoshi N, Konishi A, Wakisaka-Saito N, Suzuki R, Mugu-ruma K, Saadouni K, Sumi H, Ikawa M, Matsuoka Y, Okabe M, Sakoda S et al (2008) Genome-wide linkage analysis of a Parkinsonian-pyramidal syndrome pedigree by 500 K SNP arrays. Am J Hum Genet 82(6):1375–1384

Sidransky E (2004) Gaucher disease: complexity in a “simple” disorder. Mol Genet Metab 83(1):6–15

Silvera D, Arjü R, Darvishian F, Levine PH, Zolfaghari L, Gold-szmidt A, Maselli V, Tegnér J, Gomez-Cabrero D, Altobelli G, Emmett W et al (2011) ParkDB: a Parkinson’s disease gene expression database. Database 2011:bar007. https://doi.org/10.1093/database/bar007

Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126(4):663–676

Tan E, Schapira A (2010) Summary of GIGYF2 studies in Parkinson’s disease: the burden of proof. Eur J Neurol 17(2):175–176

Tan J, Zhang T, Jiang L, Chi J, Hu D, Pan Q et al (2011) Regulation of intracellular manganese homeostasis by Kufr–Kareb syndrome-associated ATP1A2 protein. J Biol Chem 286(34):29654–29662

Tanaka K, Suzuki T, Hattori N, Mizuno Y (2004) Ubiquitin, proteasome and parkin. BBA-Mol Cell Res 1695(1):235–247

Thomas RE, Andrews LA, Burman JL, Lin WY, Pallanck LJ (2014) PINK1-Parkin pathway activity is regulated by degradation of PINK1 in the mitochondrial matrix. PLoS Genet 10(5):e1004279

Tofaros GK (2012) Lysosome-dependent pathways in neurodegeneration as a unifying theme in Parkinson’s disease. Mov Disord 27(11):1364–1369

Trempre JF, Sauvé V, Gnenier K, Seirafi M, Tang MY, Ménade M et al (2013) Structure of parkin reveals mechanisms for ubiquitin ligase activation. Science 340(6139):1451–1455

Tsika E, Glauser L, Moser R, Fiser A, Daniel G, Sheerin UM et al (2014) Parkinson’s disease-linked mutations in VPS35 induce dopaminergic neurodegeneration. Hum Mol Genet 23(17):4621–4638

Valente EM, Abou-Sleiman PM, Caputo V, Muqit MM, Harvey K, Gispert S et al (2004) Hereditary early-onset Parkinson’s disease caused by mutations in PINK1. Science 304(5674):1158–1160

Vargas MR, Johnson JA (2009) The Nf2–ARE cytoprotective pathway in astrocytes. Expert Rev Mol Med 11

Vecchio A, Marchese A, Henry P, Rotin D, Morrione A (2003) The Grb10/Neidd complex regulates ligand-induced ubiquitination and stability of the insulin-like growth factor I receptor. Mol Cell Biol 23(9):3363–3372

Velayati A, Yu WH, Sidransky E (2010) The role of glucocerebrosidase mutations in Parkinson disease and Lewy body disorders. Curr Neurol Neurosci Rep 10(3):190

Velayos-Baeza A, Vettori A, Copley RR, Dobson-Stone C, Monaco A (2004) Analysis of the human VPS13 gene family. Genomics 84(3):536–549

Venderova K, Park DS (2012) Programmed cell death in Parkinson’s disease. Cold Spring Harb Perspect Med 2(8):a003765

Verstraeten A, Theuns J, Van Broeckhoven C (2015) Progress in unraveling the genetic etiology of Parkinson disease in an era. Trends Genet 31(3):140–149

Vilarino-Güell C, Raiput A, Milnerwood AJ, Shah B, Sza-Tu C, Trinh J et al (2014) DNAJC13 Mutations In Parkinson Disease. Hum Mol Genet 23:1794–1801

Vilarino-Güell C, Wider C, Ross OA, Dachsel JC, Kachergus JM, Lin-cohn SJ et al (2011) VPS35 mutations in Parkinson disease. Am J Hum Genet 89(1):162–167

Vingill S, Brockelt D, Lancelin C, Tatenhorst L, Dountcheva G, Preis-inger C et al (2016) Loss of FBX07 (PARK15) results in reduced proteasome activity and models a parkinsonism-like phenotype in mice. EMBO J 35(18):2008–2025

Vives-Bauza C, Zhou C, Huang Y, Cui M, de Vries RL, Kim J et al (2003) Functional interaction of Parkinson’s disease-associated LRRK2 with members of the dynamin GTPase superfamily. Hum Mol Genet 12(8):2055–2077

Stefanis L (2012) α-Synuclein locus triplication causes Parkinson’s disease. Science 305(5646):841–844

Singleton AB, Farrer MJ, Bonifati V (2013) The genetics of Parkin-son’s disease: progress and therapeutic implications. Mov Disord 28(1):14–23

Song Z, Chen H, Fiket M, Alexander C, Chan DC (2007) OPA1 processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Ym1/EL. J Cell Biol 178(5):749–755

Stafa K, Tsika E, Moser R, Musso A, Glauser L, Jones A et al (2013) Functional interaction of Parkinson’s disease-associated LRRK2 with members of the dynamin GTPase superfamily. Hum Mol Genet 22(8):2055–2077

Stefanis L (2012) α-Synuclein in Parkinson’s disease. Mutat Res 711(1):177–195

Stensson PD, Mort M, Ball EV, Evans K, Hayden M, Heywood S et al (2017) The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. Hum Genet 1–13

Stern MB, Lang A, Poewe W (2012) Toward a redefinition of Parkinson’s disease. Mov Disord 27(1):54–60

Strauss KM, Martins LM, Plun-Favreau H, Marx FP, Kautzmann S, Berg D et al (2005) Loss of function mutations in the gene encoding Omi/HtrA2 in Parkinson’s disease. Hum Mol Genet 14(15):2099–2111

Su YC, Qi X (2013) Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. Hum Mol Genet 22(22):4545–4561

Sulzer D (2007) Multiple hit hypotheses for dopamine neuron loss in Parkinson’s disease. Trend Neurosci 30(5):244–250

Suzuki Y, Imai Y, Nakayama H, Takahashi K, Taktio K, Takahashi R (2001) A serine protease, HtrA2, is released from the mitochondria and interacts with XIAP, inducing cell death. Mol Cell 8(3):613–621
Wang X, Winter D, Ashrafi G, Schlehe J, Wong YL, Selkoe D et al (2011) PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147(4):893–906

Wang X, Yan MH, Fujioka H, Liu J, Wilson-Delfosse A, Chen SG et al (2012) LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. Hum Mol Genet 21(9):1931–1944

Whone AL, Watts RL, Stoeckl AJ, Davis M, Reske S, Nahmias C et al (2003) Slower progression of Parkinson’s disease with ropinirole versus levodopa: the REAL-PET study. Ann Neurol 54(1):93–101

Williams DR, Hadeed A, al-Din ASN, Wreikat AL, Lees AJ (2005) Kufor Rakeb disease: autosomal recessive, levodopa-responsive parkinsonism with pyramidal degeneration, supranuclear gaze palsy, and dementia. Mov Disord 20(10):1264–1271

Winner B, Jappelli R, Maji SK, Desplats PA, Boyer L, Aigner S et al (2011) In vivo demonstration that α-synuclein oligomers are toxic. Proc Natl Acad Sci USA 108(10):4194–4199

Wszolek ZK, Pfeiffer B, Fulgham J, Parisi JE, Thompson B, Uitti RJ et al (1995) Western Nebraska family (family D) with autosomal dominant parkinsonism. Neurology 45(3):502–505

Xilouri M, Brekk OR, Stefanis L (2016) Autophagy and α-synuclein: relevance to Parkinson’s disease and related synucleopathies. Mov Disord 31(2):178–192

Xu J, Zhong N, Wang H, Elias JE, Kim CY, Woldman I et al (2005) The Parkinson’s disease-associated DJ-1 protein is a transcriptional co-activator that protects against neuronal apoptosis. Hum Mol Genet 14(9):1231–1241

Xu Y, Sun Y, Ran H, Quinn B, Witte D, Grabowski G (2011) Accumulation and distribution of α-synuclein and ubiquitin in the CNS of Gaucher disease mouse models. Mol Genet Metab 102(4):436–447

Yamamoto K, Fogel AI, Wang C, van der Blik AM, Youle RJ (2014) Mitochondrial Rab GTPases govern autophagosome biogenesis during mitophagy. Elife 3:e01612

Yang Z, Klionsky DJ (2010) Eaten alive: a history of macroautophagy. Nat Cell Biol 12(9):814–822

Yang QH, Church-Hajduk R, Ren J, Newton ML, Du C (2003) Omi/ HtrA2 catalytic cleavage of inhibitor of apoptosis (IAP) irreversibly inactivates IAPs and facilitates caspase activity in apoptosis. Genes Dev 17(12):1487–1496

Yoshida S, Hasegawa T, Suzuki M, Sugeno N, Kobayashi J, Ueyama M et al (2018) Parkinson’s Disease-linked DNAJC13 mutation aggravates alpha-synuclein-induced neurotoxicity through perturbation of endosomal trafficking. Hum Mol Genet 27:823–836

Yoshino H, Tomiyama H, Tachibana N, Ogaki K, Li Y, Funayama M et al (2010) Phenotypic spectrum of patients with PLAG26 mutation and PARK14-linked parkinsonism. Neurology 75(15):1356–1361

Youle RJ, Narendra DP (2011) Mechanisms of mitophagy. Nat Rev Mol Cell Biol 12(1):9–14

Yu S, Zuo X, Li Y, Zhang C, Zhou M, Zhang YA et al (2004) Inhibition of tyrosine hydroxylase expression in α-synuclein-transfected dopaminergic neuronal cells. Neurosci Lett 367(1):34–39

Yu T, Wang L, Yoon Y (2015) Morphological control of mitochondrial bioenergetics. Front Biosci 20:229

Zabetian CP, Yamamoto M, Lopez AN, Ujike H, Mata IF, Izumi Y et al (2009) LRRK2 mutations and risk variants in Japanese patients with Parkinson’s disease. Mov Disord 24(7):1034–1041

Zavodszky E, Seaman MN, Moreau K, Jimenez-Sanchez M, Breusegem SY, Harbour ME et al (2014) Mutation in VPS35 associated with Parkinson’s disease impairs WASH complex association and inhibits autophagy. Nat Commun 5

Zhang L, Shimoji M, Thomas B, Moore DJ, Yu SW, Marupudi NI et al (2005) Mitochondrial localization of the Parkinson’s disease related protein DJ-1: implications for pathogenesis. Hum Mol Genet 14(14):2063–2073

Zhong N, Kim CY, Rizzu P, Geula C, Porter DR, Pothos EN et al (2006) DJ-1 transcriptionally up-regulates the human tyrosine hydroxylase by inhibiting the sumoylation of pyrimidine tract-binding protein-associated splicing factor. J Biol Chem 281(30):20940–20948

Zhou W, Zhu M, Wilson MA, Petsko GA, Fink AL (2006) The oxidation state of DJ-1 regulates its chaperone activity toward α-synuclein. J Mol Biol 356(4):1036–1048

Zhou ZD, Sathiyamoorthy S, Angeles DC, Tan EK (2016) Linking F-box protein 7 and parkin to neuronal degeneration in Parkinson’s disease (PD). Mol Brain 9(1):41

Zucca FA, Basso E, Cupaioli FA, Ferrari E, Sulzer D, Casella L, Zecca L (2014) Neuromelanin of the human substantia nigra: an update. Neurotox Res 25(1):13–23