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REVIEW PAPER

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

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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,

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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 (L-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

Table 1 Common familial Parkinson disease-associated genes and loci

Loci	Inheritance	Gene	Position	Protein	Disease onset	Mutations
PARK1	AD rarely 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 rarely 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
PARK17	AD	*VPS35*	16q11.2	Vacuolar protein sorting 35	Late onset	Missense; splicing
PARK18	AD	*EIF4G1*	3q27.1	Eukaryotic translation initiation factor 4 gamma, 1	Late onset	Missense; deletions; insertions
PARK19	AR	*DNAJC6*	1p31.3	DNAJ subfamily C member 6	Early onset	Missense or nonsense; splicing
PARK20	AR	*SYNJ1*	21q22.11	Synaptojanin-1	Early onset	Missense
PARK21	AD	*DNAJC13*	3q22.1	DNAJ subfamily C member 13	Early onset	Missense
PARK22	AD	*CHCHD2*	7p11.2	Coiled-coil-helix-coiled-coil-helix domain 2	Late onset	Missense
PARK23	AR	*VPS13C*	15q22.2	Vacuolar protein sorting 13C	Early onset	Missense; small deletion
–	AD for PD AR for GD	*GBA*	1q21	Glucocerebrosidase	Unclear	Missense; regulatory; splicing; small indels; deletions; insertions
–	AD	*SCA2*	12q24.1	Spinocerebellar ataxia type 2	Unclear	(CAG) three nucleotide repeat variations

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

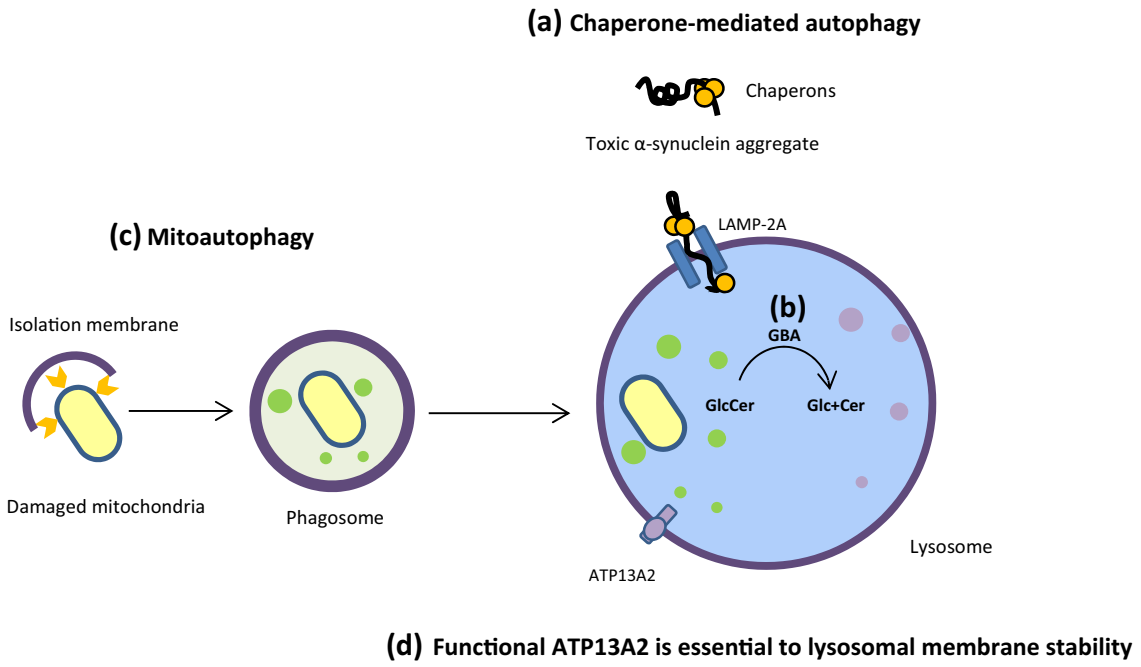

Fig. 1 Lysosome-dependent degradation pathways; As indicated, **a** toxic α-synuclein aggregates are selectively degraded within the lysosome by means of LAMP-2A and chaperones; **b** GBA catalyzes the breakdown of sphingolipid glucosylceramide to ceramide and glucose within the lysosome; **c** damaged 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

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 *PARKIN* 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 hypothesize that mutations in *PARKIN* cause a disruption in the E3

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; McLelland 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 ($\Delta\Psi$) is crucial for the direction of PINK1 towards mitochondrial membrane and for its import into mitochondrial matrix compartment. The collapse of $\Delta\Psi$ 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 unmodified 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).

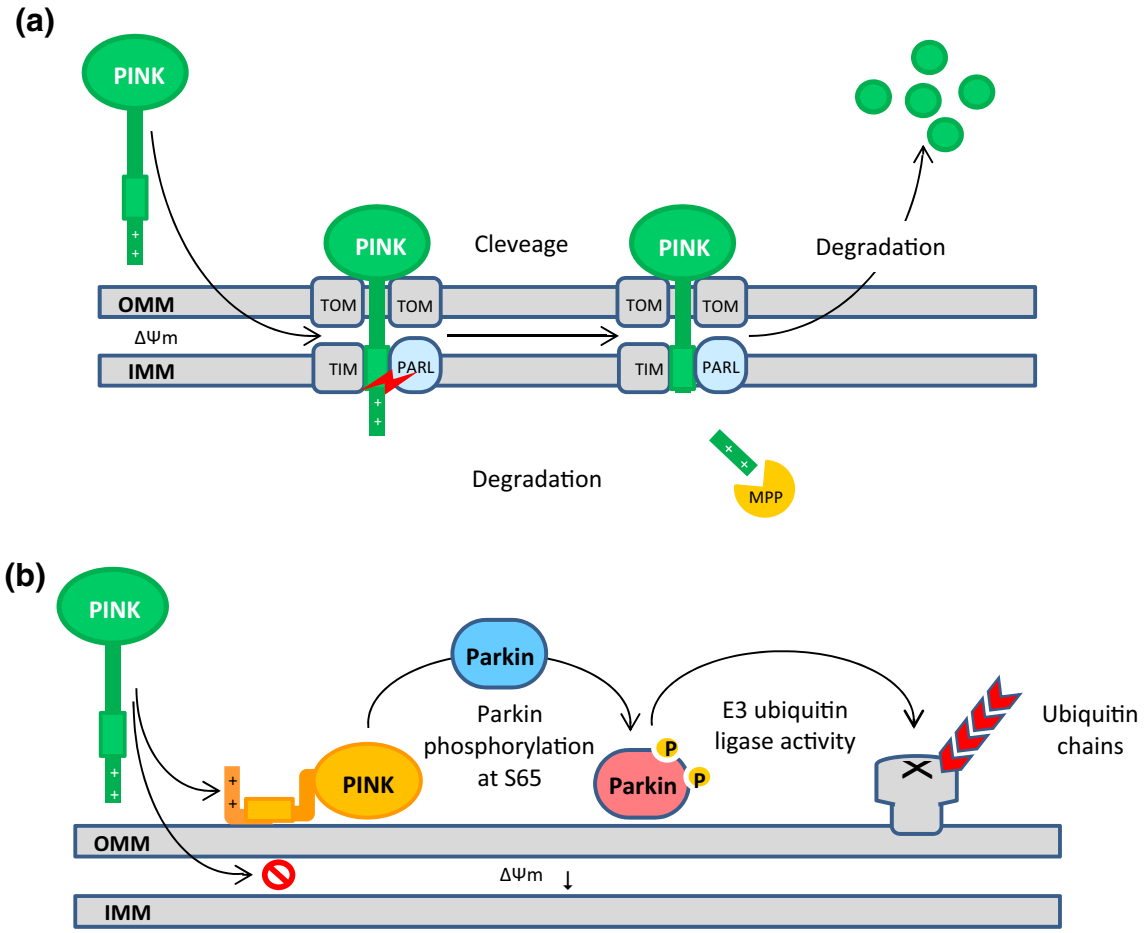

Fig. 2 **a** Mitochondrial membrane potential (ΔΨ) directs PINK1 towards OMM. PINK1 is continuously imported into mitochondria through the TOM/TIM complexes and subsequently targeting signal is cleaved and degraded by PARL and MPP, respectively. The truncated PINK1 is degraded by the ubiquitin proteasome system; **b** collapse of ΔΨ blocks the TOM/TIM import pathway. PINK1 becomes stable on the OMM and recruits Parkin and activates its E3 ubiquitin ligase activity through the phosphorylation of Parkin on Ser65

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

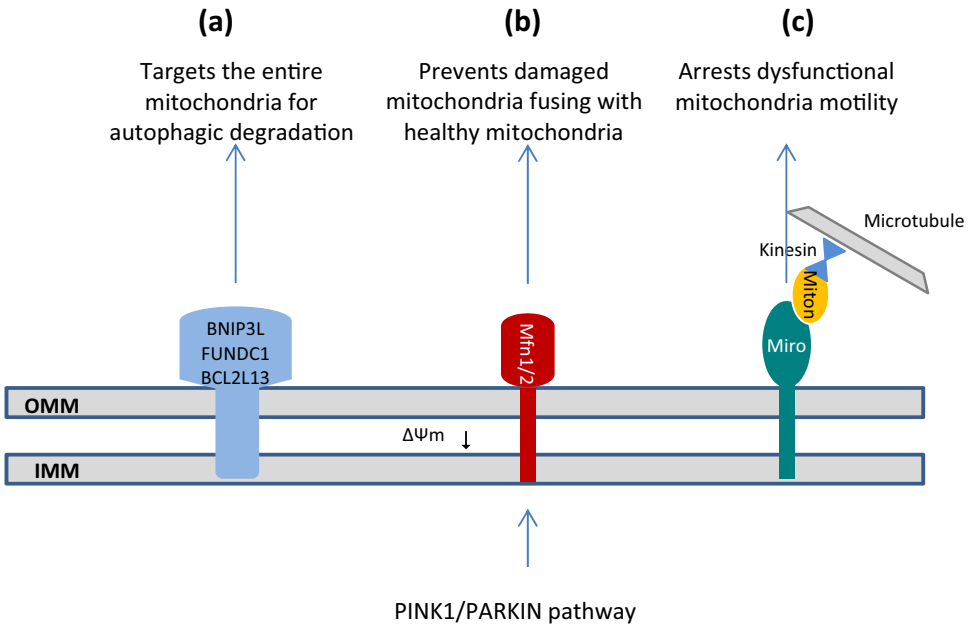

Fig. 3 Schematic representation of three pathways that PINK1/PARKIN controls hemostasis of mitochondria; **a** PINK1/PARKIN pathway targets the entire mitochondria for autophagic degradation by attaching ubiquitin chains to some outer mitochondrial membrane (OMM) proteins; **b** PINK1/PARKIN pathway induces proteasomal degradation of Mfn1/2 and isolates dysfunctional mitochondria from the healthy mitochondria; **c** PINK1/PARKIN pathway releases Milton/Kinesin complex from mitochondrial surface through the proteasomal degradation of Miro1, and leading to arrest dysfunctional mitochondria motility

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 Rab-GAPs, 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 within the neuronal cells (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, SO_2H) 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 SO_3H at cysteine 46 (C46), cysteine 53

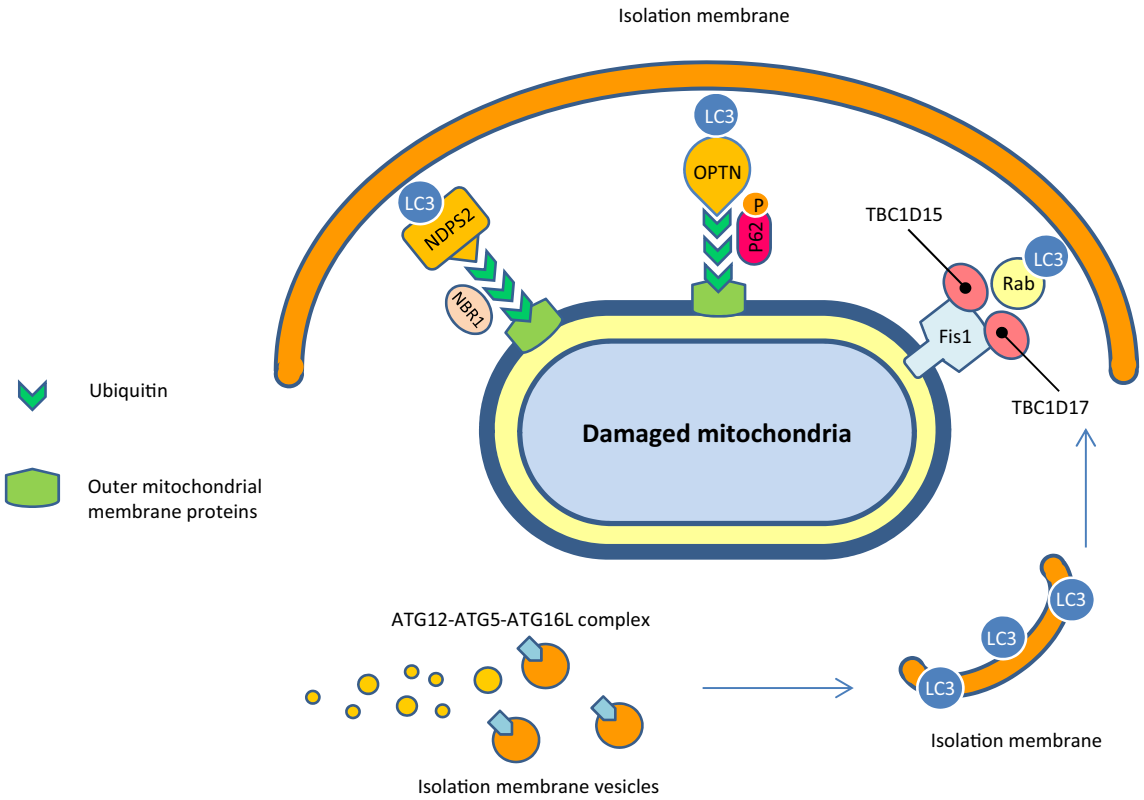

Fig. 4 Schematic representation of the phagosome membrane formation around the damaged mitochondria. Refer to the text for explanations

(C53), and 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 kinase2* (*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 *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 UCHL1 was lost (Saigoh et al. 1999). However, in neuronal cell culture and mice, the expression of UCHL1 demonstrated an increase in the level of ubiquitin within the neurons (Osaka et al. 2003). These findings led to conclude that 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 *Glucocerebrosidase* (*GBA*) gene (Grabowski 2008). Moreover, in some families affected with GD, several relatives of the probands developed Parkinsonism, many of whom were oblige heterozygous carriers of the *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 *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 *GBA* and PD was also supported by neuropathology studies, showing dopaminergic neuronal dysfunction with widespread pathologies of α-synuclein and Lewy body in patients with homozygous and heterozygous *GBA* mutation (Kono et al. 2007). In addition, detailed biochemical studies showed significant decrease in glucocerebrosidase enzyme (GCase) activity and increase in α-synuclein accumulation in PD brains, with *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 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 *GBA* mutations lead to a 20- to 30-fold increase in the risk of PD and 5–10% of PD patients have mutations in *GBA* gene (Velayati et al. 2010).

ATP13A2

Originally, *ATPase 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 5P-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 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 (Mn^{2+}) and zinc (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

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; Paisan-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 (Paisan-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; Zavodszky 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 VSP35 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 (Shojaee 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 invitro 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

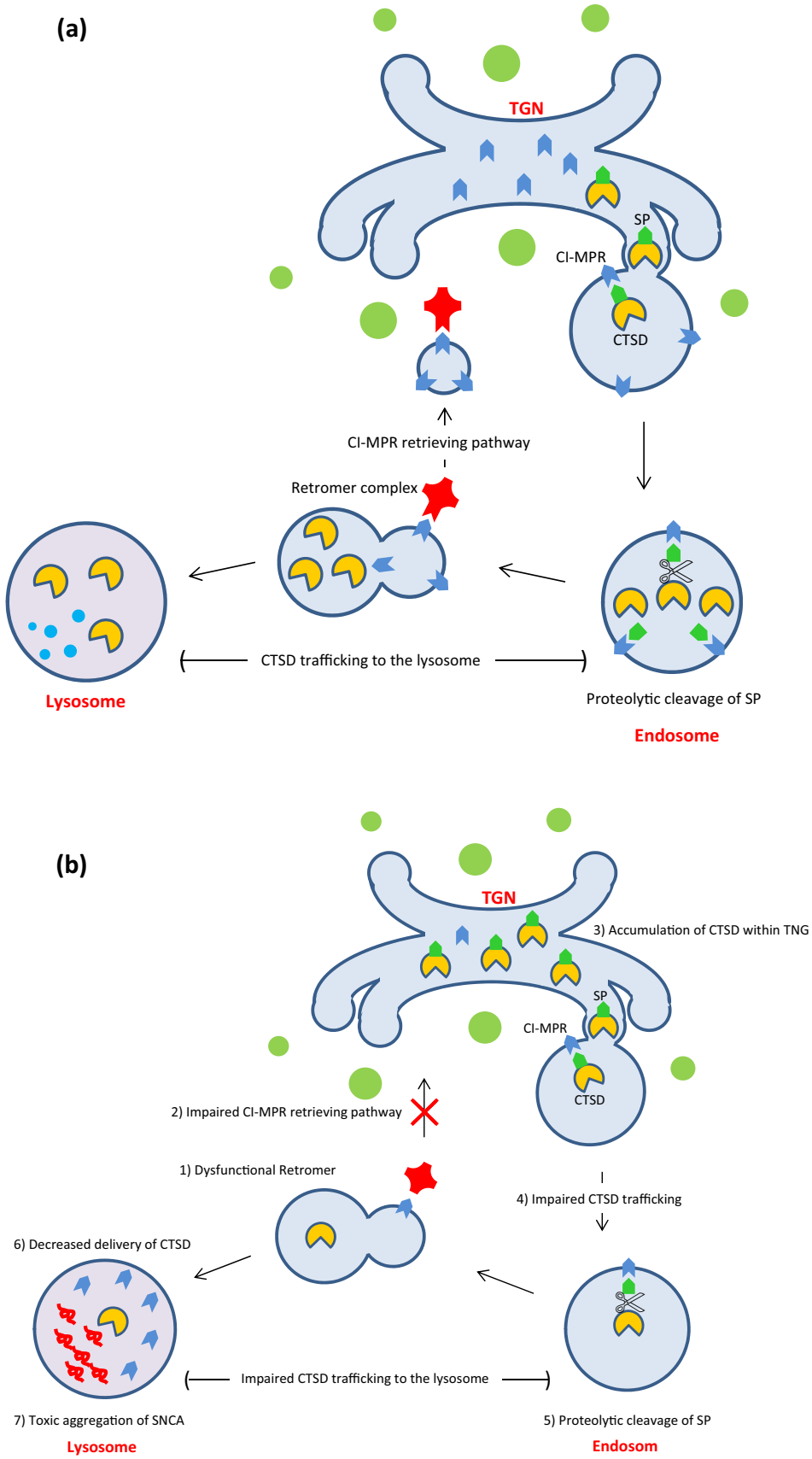

Fig. 5 **a** VPS35 is a core component of the retromer cargo-recognition complex and plays a critical role in cargo retrieving pathway from the endosome to the trans-Golgi network (TGN); **b** mutations in VSP35 cause retromer complex dysfunction and lead to decreased delivery of CTSD to the lysosome 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). *EIF4GI* 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 EIF4GI are associated with malignancy in a significant number of human breast cancers suggesting that overexpression of EIF4GI 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 *EIF4GI*-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, Overexpressing 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 nerve 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-1in 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 nonMendelian 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 $< 5 \times 10^{-8}$) 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 nonmotor 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

Table 2 GWAS meta-analyses results of the PDGene database in the populations of European descent

Gene	Polymorphism	Location	Alleles	Case–control samples	Meta OR	Meta P-value
SNCA [− 19139 bp]	rs356182	chr4:90626111	G versus A	21	1.34	1.85e-82
TMEM175	rs34311866	chr4:951947	C versus T	21	1.26	6.00e-41
STK39 [+ 24494 bp]	rs1955337	chr2:169129145	T versus G	21	1.21	1.67e-20
TMEM229B	rs1555399	chr14:67984370	T versus A	15	1.15	5.70e-16
LRRK2	rs76904798	chr12:40614434	T versus C	21	1.16	4.86e-14
BCKDK	rs14235	chr16:31121793	A versus G	21	1.10	3.63e-12
MIR4697 [− 3032 bp]	rs329648	chr11:133765367	T versus C	21	1.11	8.05e-12
INPP5F	rs117896735	chr10:121536327	A versus G	13	1.77	1.21e-11
RIT2	rs12456492	chr18:40673380	G versus A	21	1.10	2.15e-11
GCH1	rs7155501	chr14:55347827	A versus G	15	1.12	1.25e-10
SIPA1L2	rs10797576	chr1:232664611	T versus C	21	1.13	1.76e-10
TMPRSS9 [− 26450 bp]	rs62120679	chr19:2363319	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) (Büning 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.

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Compliance with Ethical Standards

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

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