The Role of Autophagy-Lysosomal Pathway Dysfunction in Parkinson's Disease: A Genetic Perspective

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Abstract

In recent years, multiple lines of evidence from human genetic and molecular studies have highlighted the importance of the autophagy lysosomal pathway (ALP) in Parkinson's disease (PD). Genes such as *GBA* and *LRRK2*, which harbor some of the most common mutations associated with PD, have essential roles in the ALP. α-synuclein, encoded by the *SNCA* gene, is degraded mainly by the ALP, and mutations/multiplications in *SNCA* may lead to impairment of chaperone mediated autophagy or other ALP functions. Numerous other PD-related genes, such as *PARK2, PINK1, TMEM175, SMPD1, CTSD, CTSB* and many more, have also been reported to have important roles in the ALP. Understanding the relationship between ALP impairment and PD pathogenesis may be crucial for uncovering the mechanisms underlying PD, and for the development of long-awaited neuroprotective therapies. In this review, we will discuss the data linking the ALP to PD (other, atypical forms of Parkinsonism, will not be discussed in this review). We will focus on evidence from studies on specific genes and proteins, their roles in the ALP, and the potential mechanisms underlying the involvement of these genes in PD.

Introduction: The lysosome as a degradation and recycling organelle

Lysosomes are membranous organelles with an acidified milieu (pH ~4.5), containing digestive enzymes such as proteases, lipases, glycosidases, nucleases and sulfatases. The lysosome is the central organelle in the autophagy lysosomal pathway (ALP), which is crucial for the maintenance of cellular homeostasis, by degrading proteins, lipids, organelles and other cellular and extracellular components[1].

Autophagy can be divided into three main types:

1) Macroautophagy: involves the formation of cytosolic vesicles (autophagosomes) that transport their cargo to the lysosome, fuse with it to create autophagolysosomes, followed by degradation of its content. Different organelles can be degraded by macroautophagy, including mitochondria (mitophagy) and peroxisomes (pexophagy) [2].

2) Microautophagy: direct engulfment of cytosolic content, mainly small molecules, into the lumen of the lysosome, followed by their digestion[3].

3) Chaperone mediated autophagy (CMA): a highly specific type of autophagy, during which proteins containing CMA target motifs such as KFERQ or VKKDQ are unfolded by cytosolic chaperones and translocated into the lysosome for degradation via a transmembrane complex composed of the lysosome-associated transmembrane protein (LAMP2A) [4, 5].

The lipid bilayer of the lysosome is composed of a broad range of lipids, different receptors and channels. The lysosome contains more than 50 different hydrolases, dysfunction of which may lead to different lysosomal storage disorders (LSD) characterized by the progressive accumulation of undegraded substrates within the lysosome, inducing a wide range of clinical symptoms. LSDs,

as a group, are relatively common, with an incidence rate of approximately 1/5000 newborns[6-8]. Most of these LSDs present with neurological manifestations, highlighting the important role of the ALP in the nervous system. This is mainly because neurons have unique characteristics, physiology and biology, which require tight regulation of cellular processes, such as their length, the lack of cell division and their complex interactions with other cells[9, 10]. Based on human genetic data, it is hypothesized that dysfunction of the ALP plays a central role in PD[11]. Mutation and variants in numerous genes play a role in PD pathogenesis, and more than 40 genes associated with PD are also involved in the ALP[11, 12] (Tables 1 and 2). In this review, we will summarize some of the most important aspects of lysosomal dysfunction in PD and discuss the potential mechanisms by which mutations in PD-related genes may impair the ALP.

Data included in the review

This review includes data mainly from human genetic studies, but also from human-based cell models, animal models, animal-based cell models, and *in vitro* study. For brevity, the model used was not always detailed, therefore it is important to note that data from animal models and cells will not always reflect human biology. Furthermore, data from human genome-wide association studies (GWAS) typically show relatively small effects of genetic variants, and it is often unclear which of the genes in each genetic locus is actually involved in PD.

Degradation of α-synuclein by autophagy

α-synuclein is a major component of Lewy-bodies, the pathological hallmark of PD, and its accumulation is thought to take part in the pathogenesis of PD[13]. Furthermore, point mutations

and multiplications of the *SNCA* gene, encoding α-synuclein, may lead to PD[14]. The two main pathways for protein degradation in cells are the ubiquitin proteasomal systems (UPS) and the ALP. It was shown that α-synuclein can be degraded by both mechanisms[15], however, while the ALP is required for α-synuclein degradation (i.e. if it is inhibited, α-synuclein will accumulate), the UPS is not essential for α-synuclein degradation (i.e. UPS inhibition does not result in α-synuclein accumulation) in neuronal cells[16]. Both intra- and extracellular α-synuclein can be degraded by the ALP, and a recent review has discussed these pathways in detail[17].

Intracellular α-synuclein is thought to be degraded by both CMA and macroautophagy. α-synuclein contains the CMA VKKDQ motif. Thus, CMA has a central part in α-synuclein degradation, and PD-causing mutations such as p.A30P and p.A53T impair the autophagy of α-synuclein by CMA[5]. One of the potential explanations for the fact that dopaminergic neurons are more vulnerable in PD, is that dopamine can modify α-synuclein and lead to its impaired degradation through CMA[18]. the degradation of α-synuclein by macroautophagy is likely a compensatory mechanism for CMA dysfunction[16], and it was suggested that increasing macroautophagy can increase the degradation of WT and mutated α-synuclein[15]. It was also demonstrated that extracellular α-synuclein, as well as α-synuclein-containing exosomes, can be uptaken by different types of cells, including neurons, astrocytes and microglia, and proceed to lysosomal degradation[17]. However, the evidence for exosomal involvement in PD still preliminary, and its role in PD needs to be further studied.

Within the lysosome, specific cathepsins, including cathepsins B, D and L, degrade α-synuclein[19]. The genes that encode both cathepsins B and D (*CTSB* and *CTSD*) were implicated in genetic studies of PD; *CTSB* is found in one of the GWAS loci[20], and *CTSD* was suggested

in a study that examined the burden of rare variants in lysosomal genes in PD patients vs. controls[21]. In transgenic mouse model, it was suggested that these cathepsins may be responsible for C-terminal truncation of α-synuclein and creation of toxic species[22]. Therefore, it can be hypothesized that genetic variants that lead to reduced ability of these cathepsins to degrade α-synuclein may lead to its accumulation. Overall, it is likely that genetic variants that lead to some impairment of the ALP in general, and specific ALP pathways involved in PD, will result in increased risk for α-synuclein accumulation. Examples of the most important PD-related genes and their potential effects on the ALP and α-synuclein accumulation will be discussed in the next sections of this review.

GBA mutations, lysosomal function and Parkinson's disease

Bi-allelic mutations in *GBA* cause Gaucher disease (GD), an autosomal-recessive lysosomal storage disorder, and clinical observations have suggested that individuals with GD may be at increased risk for PD[23, 24]. In recent years, it has been demonstrated that *GBA* has an important role in most major synucleinopathies, including PD, dementia with Lewy-bodies (DLB) and REM sleep behavior disorder (RBD), yet its role in multiple system atrophy is still not clear[25-30]. Large-scale genetic studies, including genome-wide association studies (GWAS)[20, 31, 32], have demonstrated that heterozygous *GBA* variants and mutations are strongly associated with PD, found in 5-20% of PD patients in different populations[28, 30, 33-35]. The types of *GBA* mutations, which can be defined as "severe" or "mild" based on its association with GD[30], have a differential effect on risk, onset and progression of PD. Mutations defined as "Severe" (e.g., p.L444P, p.D409H, c.84GG) have a higher risk for PD (OR=10.3) compared to "mild" mutations (e.g., p.N370S, p.R496H, OR=2.3) [36]. Common variants such as p.T369M and p.E326K do not

lead to GD even in the homozygous state, but are associated with increased risk for PD with ORs of 1.78 and 1.99, respectively [36, 37]. The type of mutation, including common variants, also impacts the age at onset (AAO) and clinical progression, and "severe" mutations lead to an earlier AAO and higher risk for cognitive decline, depression and anxiety [30, 38-41]. Overall, these effects on risk are much smaller than the effects of disease-causing mutations in other genes linked to PD. The activity of the lysosomal enzyme encoded by *GBA*, β-glucocerebrosidase (GCase), is reduced in blood, CSF and brain of patients with *GBA* mutations, and interestingly, in a subset of patients without *GBA* mutations[42-45]. This may suggest that GCase deficiency, for unknown reasons that are not *GBA* mutations, may have a role in sporadic PD, at least in a subgroup of patients.

The specific mechanism by which *GBA* mutations lead to PD is still not fully understood, yet several mechanisms have been suggested (Figure 1). In some of these mechanisms, direct or indirect interactions between α-synuclein and *GBA*/GCase have been proposed. Unlike other genetic forms of PD (e.g. *LRRK2*[46, 47], *PRKN* [parkin][48]), neuropathological studies in *GBA*-associated PD have consistently shown α-synuclein accumulation[44, 49-51]. It was further demonstrated in cellular and animal models, that GCase deficiency leads to accumulation of α-synuclein[52-56]. When active, GCase is located within the lysosome on the surface of the membrane and degrades glycolipids within the lysosomal membrane[57]. Hence, one of the hypotheses is that changes in the composition of the lysosomal membrane may affect the internalization of α-synuclein into the lysosome for degradation (Figure 1A). Since the receptor for CMA of α-synuclein, LAMP-2A, requires specific membrane composition to be active, it is possible that CMA of α-synuclein will be impaired as a result of *GBA* deficiency[11]. It was further hypothesized that changes to the lysosomal membrane may also affect other processes, such as

macroautophagy and mitophagy[11]. Supporting this hypothesis is the recent observation that GCase deficiency may indeed lead to impairment of mitophagy (Figure 1C)[58], which may induce oxidative stress and cell death. However, it is still not clear if this impairment occurs as a result of changes in the composition of the lysosomal membrane.

There are different and sometimes contradicting results regarding the accumulation of specific glycolipid substrates in GCase deficiency in PD. Some studies suggested that accumulation of glucosylceramide is potentially responsible for the development of PD (Figure 1B) in these patients[59] (which is the basis for the clinical trial for substrate reduction therapy in PD, targeting accumulation of glucosylceramide, ClinicalTrials.gov Identifier: NCT02906020). However, other studies have shown that another substrate of GCase, glucosylsphingosine, may accumulate and promote α-synuclein aggregation[56, 60]. Of note, accumulation of either of these lipids will potentially affect the composition of the lysosomal membrane and its ability to internalize α-synuclein[11]. These glycolipids may also directly interact with α-synuclein[53, 56, 61], which can lead to its accumulation due to increased interaction. Other studies have suggested that different glycolipids, such as GM2 and GM3 may accumulate in PD[62, 63], and the potential roles of these gangliosides in PD should be further studied.

Another interesting study suggested a positive feedback interaction loop between α-synuclein and GCase. Mazzulli et al. demonstrated that glucosylceramide accumulation in the lysosome can directly interact with α-synuclein and lead to its accumulation, and that the accumulation of α-synuclein may inhibit the transport of GCase to the lysosome[53] (Figure 1B). Such a positive feedback loop will increasingly impair the ability of the lysosome to degrade α-synuclein. A completely different mechanism was also proposed, suggesting that *GBA* mutations

may lead to misfolding of GCase, its accumulation in the endoplasmic reticulum (ER), which may cause ER stress and cell death[64] (Figure 1D). While it is possible that this suggested mechanism is *contributing* to PD pathogenesis in carriers of certain *GBA* mutations, it is clear that this mechanism is not *necessary* for the development of PD. Since there are *GBA* null mutations (i.e., no protein is produced, such as in the case of the c.84GG mutation), in carriers of these mutations ER accumulation of GCase cannot occur, as there is no protein at all. Notably, carriers of null mutations, such as c.84dupG, have higher risk and earlier onset of PD compared to other mutations that lead to some degree of ER retention, such as p.N370S[30]. Therefore, ER retention seems to not be necessary for PD development and not associated with the severity of the disease. Other studies have suggested that GCase deficiency may lead to increase in extracellular α-synuclein[65], which may facilitate the progression of the disease in a prion-like fashion, as was recently suggested[66].

` Neuroinflammation is thought to play a substantial role in PD pathogenesis and may have a role in *GBA*-associated PD as well[67]. It was demonstrated that microglial cells can be activated by different types of proinflammatory triggers including α-synuclein aggregates and accumulation of lipids[68-70], which may lead to activation of neurotoxic reactive astrocytes[71]. A meta-analysis of studies on cytokines in PD demonstrated elevated levels of numerous cytokines, clearly pointing out towards the presence of immune response in PD[72]. In *GBA*-associated PD, different inflammatory mechanisms may be involved, including elevated cytokines, microglial activation and possibly antigen presentation (Figure 1E). It has been shown that in *GBA*-associated PD patients, there was an elevation of monocyte-associated inflammatory cytokines (including IL-8, MCP-1, MIP1β, SCF and PARC) compared to non-carriers of *GBA* variants, and the association with IL-8 was replicated in an additional cohort[73]. Previous studies in GD patients also

demonstrated elevation of different cytokines[74-76]. The association between *GBA*, cytokines and microglial activation is also supported by animal models with GCase deficiency, in which activation of microglia and neuroinflammation are prominent pathological features[77, 78]. Lastly, since the lysosome is involved in antigen processing and presentation[79], it is possible that GCase mutations and/or substrate accumulation could lead to changes in antigen presentation that contribute to PD pathogenesis, but this remains to be further studied.

Interactors and potential modifiers of *GBA* in PD.

Several lines of evidence clearly suggest that there are modifiers (whether genetic or environmental) of *GBA*-associated PD. First, most carriers of *GBA* mutations will not develop PD, and the penetrance of *GBA* mutations in PD has been demonstrated to be about 10-30%[80, 81]. These studies did not examine whether these *GBA* carriers have developed dementia, therefore this may be an underestimation of the penetrance of the mutations included in these studies. However, they also did not include the p.E326K and p.T369M variants for which penetrance is likely much lower. Second, the clinical presentation of PD in patients with *GBA* variants and mutations is highly variable, even among carriers of the exact same *GBA* mutation[30]. Lastly, the enzymatic activity in carriers of the same *GBA* mutation is variable. For example, in some carriers of the p.N370S or p.L444P mutations, the enzymatic activity is similar to the average activity seen in non-carriers[42]. Therefore, other factors must affect the penetrance, clinical presentation of *GBA*-associated PD and GCase enzymatic activity. It is essential to identify such modifiers, as it will increase our understanding of the mechanism underlying *GBA*-associated PD. Furthermore, such modifiers can be potential targets for drug development, and identifying them will allow

better genetic counseling for asymptomatic carriers of *GBA* mutations[82]. We will discuss some of these potential modifiers below.

SCARB2 encodes the Scavenger Receptor Class B Member 2, which is responsible for the transport of GCase from the Golgi apparatus to the lysosome. Variants in the *SCARB2* locus are among the strongest risk factors for PD[83-85], but the risk variants do not seem to affect the enzymatic activity of GCase[85], although it is possible that such modification exists but was too small in magnitude to be detected. Therefore, additional studies on the potential modifier effect of *SCARB2* in *GBA*-associated PD should be performed. Saposin C (SapC), encoded by *PSAP*, is a co-activator of GCase, which is required for its activity[86], and rare bi-allelic mutations in SapC may cause a disease with a GD-like phenotype. Recent study in which *PSAP* was fully sequenced in PD patients failed to detect an association between *PSAP* and PD[87]. Since GD-causing mutations in *PSAP* are rare and were not detected by in this study, analyses of larger cohorts are necessary.

TMEM175 encodes a lysosomal potassium channel, and a coding variant (p.M393T) in this gene represents the fourth-strongest (in terms of genetic association) common risk factor for PD, after variants in the *SNCA*, *GBA* and *LRRK2* loci[20]. Very recently, it was shown that this variant may affect the activity of GCase in cellular models[88]. Furthermore, in the same study, TMEM175 was shown to be involved in the regulation of lysosomal pH, which is essential for GCase activity. This observation may provide a potential mechanism, where variants in TMEM175 change the pH of the lysosome, which in turn can reduce GCase activity and possibly lead to α-synuclein aggregation. Previous studies suggested that variants in the *MTX1* gene[89] and *BIN1* locus[90] (a known Alzheimer's disease locus) may affect the AAO of GBA-associated PD. However, these results await further replication.

Recently, a GWAS comparing PD patients with *GBA* variants to controls with *GBA* variants identified variants in the *SNCA* and *CTSB* loci as modifiers of *GBA* penetrance, and variants in the *SNCA* and the *TMEM175* p.M393T variant affect the AAO of *GBA*-associated PD[91]. Additional studies on these genes are required to understand the mechanisms underlying these effects.

Lysosomal genes in the glycosphingolipid metabolism pathway in PD

Interestingly, several genes that work in parallel, upstream or downstream to *GBA* in the lysosomal glycosphingolipid metabolism pathway have also been implicated in PD by human genetic and human enzymatic data (Figure 2). Bi-allelic mutations in these genes also cause LSDs, and they include *SMPD1* (Niemann-Pick type A/B disease), *GALC* (Krabbe disease), *ASAH1* (Farber disease / spinal muscular atrophy with progressive myoclonic epilepsy) and *GLA* (Fabry disease). Rare *SMPD1* mutations have been suggested to be involved in PD in multiple studies[92-95], and recently it was suggested that decreased activity of acid sphingomyelinase, the enzyme encoded by *SMPD1*, is associated with earlier AAO of PD. Furthermore, in human cell models, *SMPD1* deficiency led to α-synuclein accumulation[96]. *GALC* was implicated in PD by GWASs, with a significantly associated SNP (rs979812) at the 5' region of the gene[20]. This SNP is associated with the expression of *GALC*, including in some brain tissues (GTEx - www.gtexportal.org/home/).One of the end products of *GBA*, *SMPD1* and *GALC* activity is ceramide (Figure 2), which may implicate it in the pathogenesis of PD, as was previously suggested[97-99]. Furthermore, burden of rare mutations in *ASAH1*, which is downstream to *GBA*, *SMPD1* and *GALC* and degrades ceramide, was also associated with PD in a large sequencing

study[21]. Lastly, the X-linked *GLA* gene was not directly shown to be involved in PD, yet the enzymatic activity of alpha galactosidase A, encoded by *GLA*, was reduced in PD patients compared to controls[100]. In a small study of parents of Fabry patients, the age-specific risk for PD at age 70 was ~11%, and there was an increased prevalence of PD in first-degree relatives of the patients or their parents who are obligated carriers[101]. However, these results should be taken with caution, as they were based on a small study, and larger studies including sequencing of *GLA* in large PD cohorts should be performed to determine whether *GLA* is involved in PD. Nevertheless, the clustering of five PD related genes/enzymes within this pathway suggests that it may be one of the central pathways involved in the pathogenesis of PD. The main gap is to identify the exact imbalance within this pathway, which then can be addressed as a potential target for treatment.

LRRK2 **and related genes (*VPS35, RAB29/RAB7L1*) and their effects on the ALP**

Leucine-rich repeat kinase 2 (encoded by *LRRK2*) is a large, multi-domain protein (Figure 3), in which mutations (e.g. p.G2019S, p.R1441C/H/G and more), associated with increased kinase activity, have been shown to cause PD[102-106]. In addition, common coding variants in *LRRK2* were associated with reduced risk for PD and RBD[107, 108]. However, post mortem studies of PD patients who carried *LRRK2* mutations have demonstrated that in many of the patients there was no evidence for α-synuclein pathology. Neuropathological analysis of 37 patients with *LRRK2* mutations revealed that in 20 of them (54%), Lewy bodies were absent[109]. While Lewy bodies were found in 65% (11/17) of carriers of the p.G2019S mutation, they were found in only 11% (1/9) of those with the p.I2020T mutation. This may suggest that the mechanism underlying

LRRK2-associated PD could be different, although there is evidence suggesting that it may also include the ALP[110, 111].

Numerous suggested mechanisms for *LRRK2*-associated PD have been proposed, with multiple studies suggesting different mechanisms in different models (Figure 3). These include (partial list from recent years only): disruption of synaptic vesicle trafficking[112], cell death induced by advanced glycation end products[113], inhibition of miRNAs[114], inflammatory response[115], decreased ciliation[116], upregulation of the p53-p21 pathway[117] mitochondrial fission and TNFα-mediated neuroinflammation[117] and many others (Figure 3). Furthermore, even regarding α-synuclein there are contradicting results, as some studies suggested that LRRK2 activity affects α-synuclein accumulation[118] while other studies demonstrated that it did not[119]. It is therefore difficult to determine which LRRK2-related pathways are indeed important for PD, and if these models are relevant at all for human PD research. Nevertheless, there are accumulating data suggesting that ALP dysfunction may take a part in *LRRK2*-associated PD[102, 110, 111], and various studies suggest that one of the main roles of *LRRK2* could be phosphorylation of Rab proteins (reviewed in[120]). It was recently shown that RAB29 (formerly RAB7L1, encoded by *RAB29*, a risk locus for PD[121]) can recruit LRRK2 to stressed lysosomes, which then phosphorylates other Rabs including Rab8 and Rab10, to maintain lysosomal homeostasis[122]. Similar interactions between *RAB29* and *LRRK2* that may affect the ALP function have been suggested in other studies as well[24, 123-125], further strengthening the potential importance of this specific pathway in PD. Interestingly, another PD-related gene, *VPS35*[126], may also be involved in this pathway[127-130]. Rare mutations in *VPS35* may cause autosomal-dominant PD[126], and the PD-causing mutation p.D620N has been shown to increase the phosphorylation of Rabs by LRRK2[127]. It was further demonstrated that the WT VPS35

protein, but not the mutated protein, rescued endolysosomal defects caused by mutations in *LRRK2* and *RAB29*[128]. Additional studies have suggested that *VPS35* mutations may impair macroautophagy[131] or CMA[132]. Therefore, it seems that these three PD-related proteins may act in concert, perhaps together with additional Rabs, in maintaining proper function of the ALP and endolysosomal trafficking.

Recessive PD genes and their involvement in mitophagy

Several genes have been implicated in rare forms of autosomal-recessive, early-onset PD (EOPD), including *PRKN* (formerly *PARK2*, Parkin)[133], *PINK1*[134], *PARK7* (DJ-1)[135] and *VPS13C*[136]. Other recessive genes that cause atypical forms of Parkinsonism will not be discussed in this review. Interestingly, all four genes are involved in mitochondrial maintenance and mitophagy. When mitochondria are damaged / depolarized, PINK1 is recruited to the mitochondria, and its kinase activity phosphorylates the ubiquitin-like domain of Parkin, which activates mitophagy[137-139]. DJ-1 works in a parallel pathway to that of PINK1/Parkin and can rescue the phenotype in PINK1-deficient *drosophila*[140]. Mutations in these three genes may therefore impair mitophagy, and a systematic review of >5,800 EOPD cases, has shown that the total frequencies of mutations in *PRKN*, *PINK1*, and *PARK7* were 8.6%, 3.7%, and 0.4%, respectively[141].

More recently, bi-allelic mutations in *VPS13C* were demonstrated to cause rapidly progressive EOPD/parkinsonism, with extensive α-synuclein pathology[136]. *VPS13C* deficiency led to changes in mitochondrial morphology, impairment of the mitochondrial transmembrane potential and respiration, and to activation of the PINK1/Parkin pathway for mitophagy[136]. Another study suggested that VPS13C may be a lipid transporter that can act between the ER and the lysosome[142]. Unlike *PRKN*, *PINK1* and *PARK7*, the *VPS13C* locus was reported in

GWASs[20], and a coding haplotype with a potential protective effect has also been recently described[143]. Overall, the involvement of these four genes in rare forms of EOPD, and their role in mitochondrial function and mitophagy, emphasize that this pathway is important in specific forms of PD, and perhaps in PD generally.

Genome-wide association studies of Parkinson's disease highlight the autophagy-lysosomal pathway

In a previous review, we summarized findings from GWASs that link genes within PD-associated loci and the ALP[11]. These included genes such as *RAB29*, *MAPT*, *SREBF1*, *LAMP3*, *GAK*, *SCARB2*, *TMEM175*, *GPNMB* and more, all involved in different aspects of the ALP, as reviewed here and previously[11]. Since then, a much larger GWAS has been published, with ~40,000 cases and ~1.4M controls, further highlighting the potential role of the ALP by identifying numerous other loci with genes involved in this pathway[20]. Enrichment analysis performed in this GWAS revealed that pathways related to lysosomal function are at the top of the significantly enriched pathways. Furthermore, at least three genes involved in LSDs were implicated in this GWAS (*GUSB*, *GRN*, and *NEU1*), and additional genes in different loci, as summarized in Table 2 (a version of this table with a full reference list can be found in the Supplementary Material), are involved in different functions within the ALP. Prominent examples, on top of *CTSB*, *GALC* and others that were mentioned in earlier parts of this review, are: *BAG3*, which modulates selective autophagy of misfolded proteins[144], *SH3GL2*, encoding Endophilin-A, which is involved in autophagosome formation in the brain[145] and *HIP1R*, which regulates vesicle budding and transport, has been recently shown to target specific proteins for lysosomal degradation[146].

A different GWAS that was focused on genetic variants that affect the AAO of PD, has also demonstrated that loci associated with AAO include genes that are involved in the ALP. Significant effects on AAO were associated with the loci of *SNCA*, *TMEM175*, *GBA*, *SCARB2*, *LAMP3* and *BAG3*[84], all ALP-related genes. Considered together, these GWASs demonstrate the important role of ALP-related genes in risk and onset of PD.

Other lysosomal genes potentially involved in PD

Several other lysosomal and ALP-related genes have also been suggested to be involved in PD, yet their association with the disease needs to be further studied. These mainly include *ARSA* and *NPC1*. Recently, variants in Arylsulfatase A, encoded by *ARSA*, were suggested to be risk factors or modifiers of PD, and Arylsulfatase A has been suggested to directly interact with α-synuclein[147]. Arylsulfatase A is a lysosomal enzyme, and bi-allelic *ARSA* mutations may lead to the LSD metachromatic leukodystrophy. However, since this study was based on a very small population, additional studies are needed to determine whether *ARSA* has a role in PD. Mutations in *NPC1* cause the LSD Niemann-Pick type C1 (NPC1), and a few neuropathological studies have suggested that α-synuclein may be accumulated in NPC1 patients[148, 149]. However, thus far, no convincing genetic evidence have been reported on the association between *NPC1* mutations and PD. In one study there was an increased frequency of *NPC1* mutations in patients vs. controls, but it was not statistically significant[150], and a few heterozygous carriers of *NPC1* mutations with PD have been reported[151, 152]. Here too, additional studies are required to examine whether *NPC1* is involved in PD.

Conclusion

While it is likely that other pathways also have important roles in PD, human genetic and molecular data suggest that the ALP and its dysfunction are central in PD aetiogenesis. Furthermore, the ALP has a major role in some of the other suggested pathways in PD, such as immune response, impaired trafficking and mitochondrial dysfunction. Currently, there are ongoing clinical trials in humans (e.g. on *GBA* and *LRRK2*) in phases 1 and 2, that specifically target components of the ALP and specific individuals with genetic variants in these genes, in a precision medicine approach. Better understanding of the particular mechanisms by which dysfunction of the ALP leads or predisposes to PD may allow for developing target-specific drugs that may eventually delay, stop, prevent or even cure PD.

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Figure legends.

Figure 1. Suggested pathways in *GBA*-associated PD

Figure 1 depicts potential mechanisms involved in *GBA*-associated PD, detailed in length in the text. **A)** Since GCase works on glycosphingolipids within the membrane, *GBA* mutations that affect its function may lead to changes in the composition of the lysosomal membrane. **B)** Positive feedback loop between α-synuclein accumulation and reduction of GCase function. **C)** Impaired mitophagy due to GCase dysfunction. **D)** Some *GBA* mutations result in protein misfolding and accumulation of GCase in the endoplasmic reticulum (ER). It has been suggested that this could lead to ER stress and cell death. **E)** Potential role of the neuroinflammation in *GBA*-associated PD. The specific mechanisms by which *GBA* mutations may affect these pathways is still not fully understood. Abbreviations: GluCer, glucosylceramide; α-syn, α-synuclein; ER, endoplasmic reticulum; Ag, antigen.

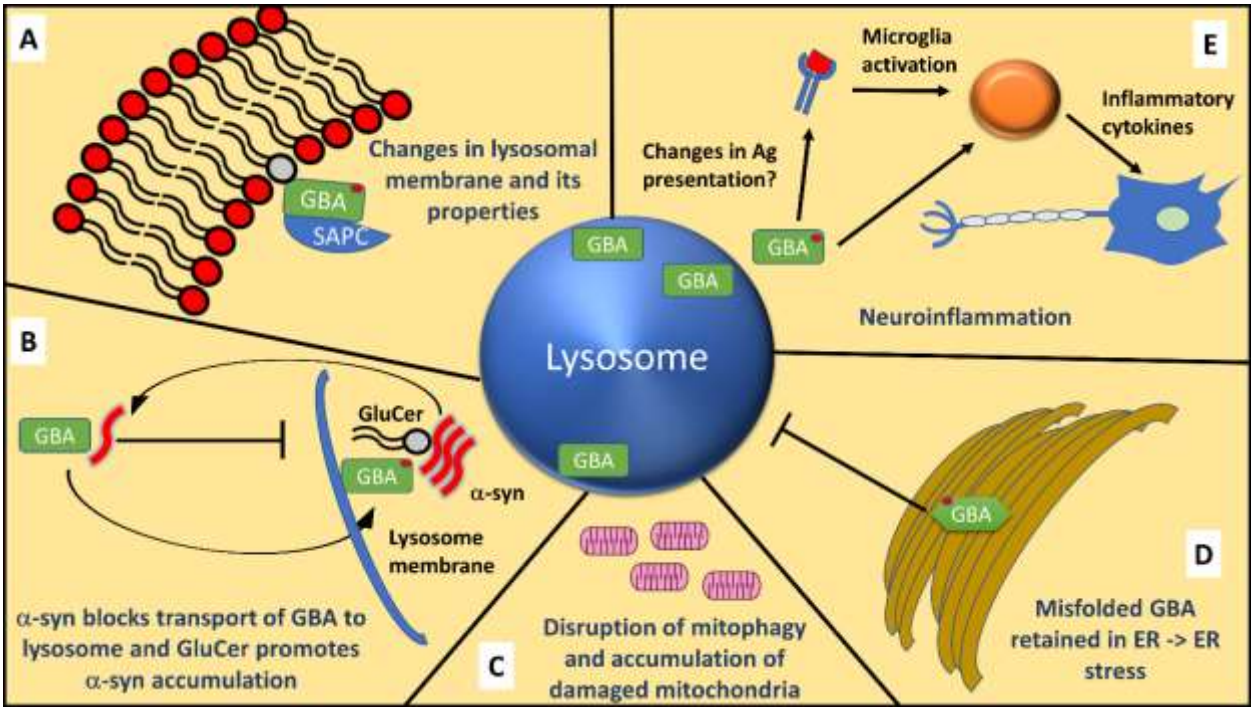


Figure 2. Genes involved in the glycosphingolipid lysosomal metabolism pathways and in PD

Figure 2 depicts a part of the lysosomal glycosphingolipid metabolism pathway, including genes encoding lysosomal enzymes (depicted in green rectangles with the names of their encoding genes) and substrates (in blue ellipsoids) potentially involved in PD. The clustering of several important PD-related genes in a small part of the pathway may suggest that it has a major role in PD pathogenesis.

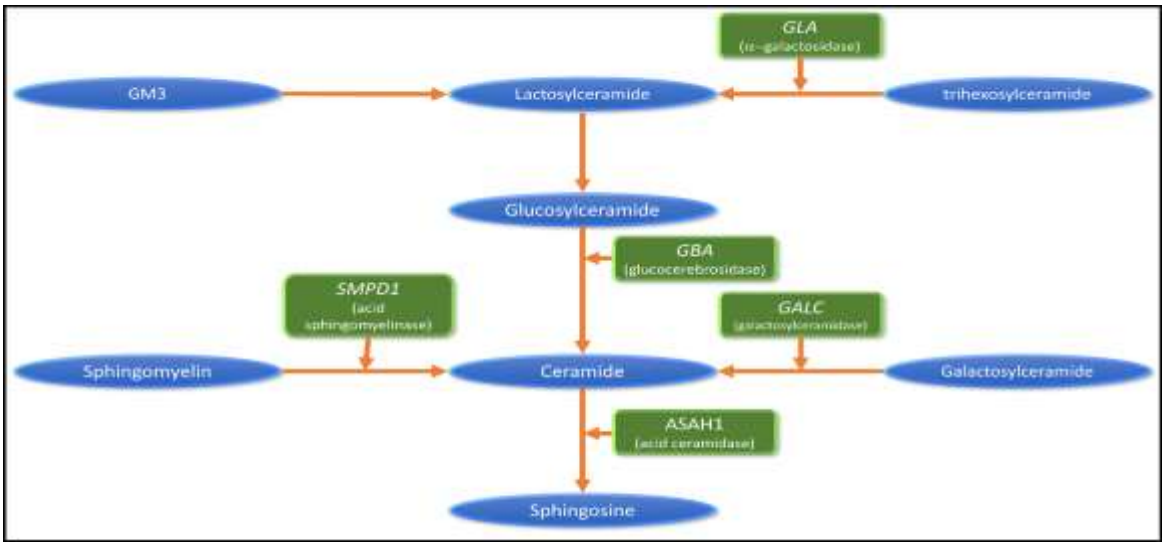
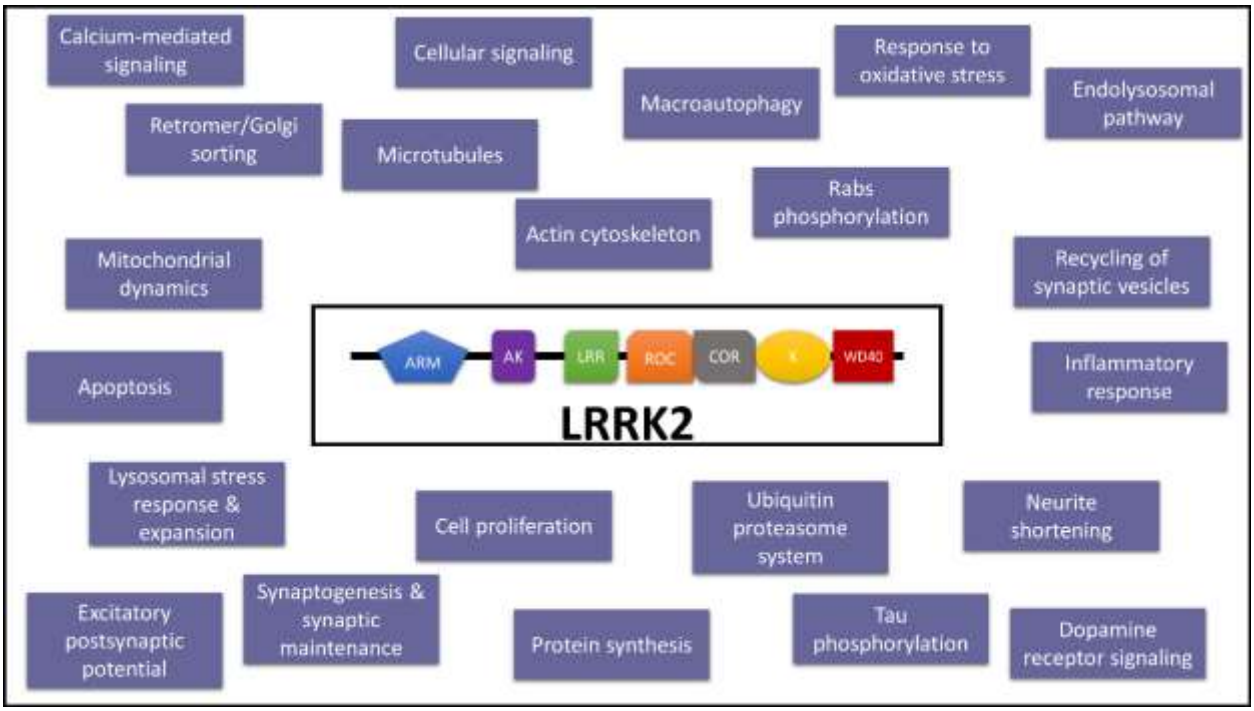


Figure 3. Mechanisms suggested to be involved in *LRRK2*-associated PD

Figure 3 depicts the domain structure of the LRRK2 protein, and the numerous mechanisms that have been suggested to be involved in *LRRK2*-associated PD. While some of these mechanisms are related to the lysosome and/or to autophagy, many others are not. The models used to study these mechanisms are often animal models, mostly rodents, which may not be relevant for human PD. Therefore, studies on human-based models are likely to shed better light on the mechanism underlying *LRRK2*-associated PD.



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Tables

Table 1. Familial and other genes involved in Parkinson's disease[a] and their roles in the autophagy-lysosomal pathway.

Gene	Genetic and clinical features	Role in ALP
Autosomal dominant PD genes		
SNCA	Rare point mutations and gene multiplication lead to EOPD, with typical features. Several point mutations and gene duplication associated with late-onset PD	Degraded by the ALP; overexpression or point mutations may lead to dysfunction of CMA, microautophagy and macroautophagy.
LRRK2	Several mutations were reported, most common is p.G2019S. Typical phenotype, with lower rates of non-motor symptoms.	Regulates endolysosomal transport, lysosomal function and potentially mitophagy.
VPS35	Very rare, only one mutation (p.D620N) was reliably confirmed as associated with PD. Typical phenotype, potentially with earlier age at onset.	Involved in endolysosomal transport regulation.
Autosomal recessive PD genes		
PRKN (Parkin)	Bi-allelic mutations are the most common recessive genetic cause of EOPD. Typical phenotype, dystonia is common, early onset but slowly progressive.	Regulates mitophagy through interaction with PINK1 and targeting of dysfunctional mitochondria for degradation by the lysosome.
PINK1	The second most common recessive genetic cause of EOPD. Typical phenotype, anxiety may be more common	Regulation of mitophagy through the same pathway as *PRKN*
PARK7 (DJ-1)	Rare cause of recessive EOPD. Typical phenotype, early onset, more dystonia at presentation	Regulation of mitophagy in a parallel pathway to that of *PRKN*/*PINK1*
VPS13C	Very rare mutations were reported. Early onset, rapidly progressive PD with rapid cognitive decline.	Activates the *PRKN*/*PINK1* mitophagy pathway.
Other genes, involved in PD and lysosomal storage disorders		
GBA	More than 100 mutations were reported in PD. Typical PD with earlier onset on average, and wide spectrum of non-motor symptoms. Prominent cognitive decline and neuropsychiatric features	A lysosomal hydrolase involved in degradation of glycosphingolipids. Bi-allelic mutations may cause Gaucher disease.
SMPD1	Rare mutations, mainly in Ashkenazi Jews, were associated with PD in	A lysosomal hydrolase involved in degradation of sphingolipids. Bi-allelic

	different studies. Typical PD, possibly with earlier onset.	mutations may cause Niemann-Pick type A/B disease.
ASAH1	Burden analysis suggested association with PD, yet this association needs to be replicated. No information on clinical presentation is available.	A lysosomal enzyme responsible for the degradation of ceramide. Bi-allelic mutations may cause Farber disease or spinal muscular atrophy with progressive myoclonic epilepsy.
GLA	No genetic evidence for involvement, yet enzymatic activity is reduced in PD patients. No information on clinical presentation is available.	A lysosomal hydrolase involved in glycolipid degradation. Bi-allelic mutations may cause Fabry disease.

ALP, autophagy lysosomal pathway; PD, Parkinson's disease; CMA, chaperon mediated autophagy; EOPD, early onset PD.

[a] Only including genes that are potentially involved in PD, not including genes that are involved in atypical parkinsonism such as *ATP13A2*, *FBXO7*, *SYNJ1*, *DNAJC6*, *PLA2G6* and others. Also not including genes that their role in PD is controversial or genes that were previously thought to be involved in PD, but are currently considered as non-causative genes in PD, such as *DNAJC13*, *UCHL1*, *GIGYF2*, *EIF4G1* and others.

Table 2. Genes in PD GWAS loci[a] and their potential roles in the autophagy lysosomal pathway[b].

Gene	Location of gene	Associated SNP	Role in ALP
GBAP1	1q22	rs76763715	May modulate *GBA* expression and activity [153]
VAMP4	1q24.3	rs11578699	Potential genetic modifier of *LRRK2* [154]
RAB29	1q32.1	rs11557080	Regulator of LRRK2 [123, 128]
SIPA1L2	1q42.2	rs10797576	Modulates maturation of lysosomes [155]
TMEM163	2q21.3	rs57891859	Plays a role in lysosomal Zn2+ uptake [156, 157]
STK39	2q24.3	rs1474055	Involved in regulation of autophagy [158]
SATB1	3p24.3	rs73038319	Indirect regulation of lysosomal and mitochondrial function through cell cycle regulation [159]
SPTSSB	3q26.1	rs1450522	Involved in sphingolipid metabolism [160]
LAMP3	3q27.1	rs10513789	Lysosomal membrane protein, involved in autophagy [161]
GAK	4p16.3	rs873786	Vesicular transport; Lysosomal enzyme sorting [125, 162]
TMEM175	4p16.3	rs34311866	Regulation of lysosomal membrane potential and maintaining pH stability [163, 164]
SCARB2	4q21.1	rs6825004	Biogenesis and reorganization of endosomes and lysosomes, Encodes the lysosomal integral membrane protein 2 (LIMP-2), a transporter of GBA [165, 166]
NEU1	6p21.33	rs9261484	Encodes Neuraminidase 1, a lysosomal enzyme that cleaves terminal sialic acid residues from glycoproteins and glycolipids [167]
FYN	6q21	rs997368	Involved in regulation of autophagy [168]
GPNMB	7p15.3	rs199351	Recruitment of LC3 recruitment to the phagosome [169, 170]
GUSB	7q11.21	rs76949143	Encodes Glucuronidase beta, a lysosomal hydrolase involved in degradation of glucuronate-containing glycosaminoglycan [171]
CTSB	8p23.1	rs1293298	Lysosomal protease, involved in the lysosomal degradation of α-synuclein [172-174]
SH3GL2	9p22.2	rs13294100	Regulates autophagosome formation in the brain [145]
GBF1	10q24.32	rs10748818	Involved in vesicular and endosomal trafficking, lipid homoeostasis [175]
BAG3	10q26.11	rs72840788	Regulation of chaperone-based aggresome targeting and selective autophagy [176-178]
SEC23IP	10q26.11 -q26.12	rs117896735	Possible involvement in cargo transport [179]
HIP1R	12q24.31	rs10847864	Involved in vesicle budding and transport; lysosomal degradation [180]
GALC	14q31.3	rs979812	Lysosomal hydrolase, degrades glycosphingolipids [181]
NOD2	16q12.1	rs6500328	Involved in initiation and modulation of autophagy [182, 183]
SREBF1	17p11.2	rs11868035	Regulates mitophagy [184]

GRN	17q21.31	rs850738	Regulates lysosomal function, chaperone of lysosomal enzymes including GCase [185-187]
MAPT	17q21.31	rs242562	Involved in the endosomal-autophagy pathway [188, 189]
CRHR1	17q21.31	rs62053943	May take part in regulation of autophagy [190]
MAP3K14 (NIK)	17q21.31	rs17686238	Regulates mitochondrial fission and trafficking [191]
NSF	17q21.31	rs199453	Promotes autophagy via SNARE complex [192]
MEX3C	18q21.2	rs8087969	Involved in exosomal sorting of specific micro-RNAs [193]
SPPL2B	19p13.3	rs55818311	Might play a role in protein aggregation, located endosomes/lysosomes (no clear role established) [194]
DDRGK1	20p13	rs2295545	Part of a complex involved in intracellular vesicle trafficking [195]

PD, Parkinson's disease; GWAS, genome-wide association study; SNP, single nucleotide polymorphism; ALP, autophagy lysosomal pathway

[a] These include the nearest genes to the GWAS associated SNP in each locus, or genes that were implicated in the specific loci by QTL or other functional analyses.

[b] Genes that are involved in both familial forms of PD and are also identified in GWAS loci are detailed in Table 1. These include *SNCA*, *GBA*, *LRRK2* and *VPS13C*.

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