

Review

Na-Young Yang, Yu-Na Lee, He-Jin Lee, Yoon Suk Kim and Seung-Jae Lee*

Glucocerebrosidase, a new player changing the old rules in Lewy body diseases

Abstract: Mutations in the gene encoding glucocerebrosidase (*GBA1*) cause Gaucher disease (GD), a lysosomal storage disease with recessive inheritance. Glucocerebrosidase (GCCase) is a lysosomal lipid hydrolase that digests glycolipid substrates, such as glucosylceramide and glucosylsphingosine. *GBA1* mutations have been implicated in Lewy body diseases (LBDs), such as Parkinson's disease and dementia with Lewy bodies. Parkinsonism occurs more frequently in certain types of GD, and *GBA1* mutation carriers are more likely to have LBDs than non-carriers. Furthermore, GCCase is often found in Lewy bodies, which are composed of α -synuclein fibrils as well as a variety of proteins and vesicles. In this review, we discuss potential mechanisms of action of *GBA1* mutations in LBDs with particular emphasis on α -synuclein aggregation by reviewing the current literature on the role of GCCase in lysosomal functions and glycolipid metabolism.

Keywords: α -synuclein; Gaucher disease; *GBA1*; glycolipid; lysosome; Parkinson's disease.

*Corresponding author: **Seung-Jae Lee**, Department of Biomedical Science and Technology, Konkuk University, Seoul 143-701, Korea, e-mail: sjlee@konkuk.ac.kr; and SMART-IABS, Konkuk University, Seoul 143-701, Korea

Na-Young Yang and Yu-Na Lee: Department of Biomedical Science and Technology, Konkuk University, Seoul 143-701, Korea

He-Jin Lee: Department of Anatomy, Konkuk University, Seoul 143-701, Korea; and SMART-IABS, Konkuk University, Seoul 143-701, Korea

Yoon Suk Kim: Department of Biomedical Laboratory Science, Yonsei University, Wonju 220-710, Korea

Introduction

Glucocerebrosidase (GCCase, Online Mendelian Inheritance in Man [OMIM] #606463), a lysosomal hydrolase, cleaves the β -glucosyl linkage of glucosylceramide (GC) and glucosylsphingosine (GS). The glucocerebrosidase gene (*GBA1*) has been mapped to 1q21-22 and is comprised

of 11 exons and 10 introns spanning 7.6 kb (Hruska et al., 2008). Approximately 300 different mutations have been discovered in *GBA1* in patients with Gaucher disease (GD) (Hruska et al., 2008), the most common lysosomal storage disease. GD is an autosomal recessive disorder of sphingolipid metabolism (Jmoudiak and Futerman, 2005). Glycolipid substrates such as GC and GS accumulate intracellularly under conditions of low GCCase, particularly in cells of mononuclear phagocyte origin. As a result, macrophages with GC-laden lysosomes, referred to as 'Gaucher cells', are produced. 'Gaucher cells' are a classic cellular hallmark of GD and are found in the liver, spleen, and bone marrow, with coincidental organomegaly (Pennelli et al., 1969; Pastores, 1997).

GD is classified into three clinical subtypes based on the age of onset, clinical signs, and the extent of central nervous system-related symptoms (Futerman et al., 2004). Type 1 GD is non-neuropathic and is the most common GD type. Although type 1 GD occurs in the general population, Ashkenazi Jews are more likely to contract type 1 GD (Hruska et al., 2008). While type 1 GD is considered non-neuropathic, a subset of patients show neurological symptoms such as parkinsonism, dementia, and subclinical peripheral neuropathy (Neudorfer et al., 1996; Biegestraaten et al., 2008; Capablo et al., 2008; Alonso-Canovas et al., 2010). Many studies have suggested a link between type 1 GD and Parkinson's disease (PD). For example, brains from patients with type 1 GD and Parkinsonism display Lewy bodies (LBs) and loss of substantia nigra (SN) neurons, which are histological signs of PD (Wong et al., 2004). Type 2 GD is acutely neuropathic and is the most severe form of GD. It often develops in infants of 6 months of age or earlier, and those afflicted with type 2 GD usually die within 2–3 years after birth. Type 3 GD is chronically neuropathic, and patients show neurological signs later than those with type 2 GD.

GD-linked mutations consist of insertions, point mutations, deletions, frame-shifts, splice junction mutations, and conversion or recombination with a downstream pseudogene (Hruska et al., 2008). The relationship between clinical phenotype and *GBA1* genotype is

unclear, as enormous clinical heterogeneity occurs in GD, even among siblings and identical twins (Goker-Alpan et al., 2005; Biegstraaten et al., 2011).

Patients with PD are five times more likely to carry *GBA1* mutations than healthy controls (Sidransky et al., 2009). Moreover, patients with type 1 GD tend to develop Parkinsonian symptoms (Neudorfer et al., 1996). Therefore, the link between *GBA1* mutations and synucleinopathies is noteworthy. In this review, we assess the implications of *GBA1* mutations in PD and related neurological diseases.

Parkinson's disease, Lewy bodies, and α -synuclein

PD is the second most frequent neurodegenerative disorder of the elderly. More than 1% of the European population >65 years and more than 4% of those >85 years are affected by this disease (de Rijk et al., 2000). PD is recognized primarily as a movement disorder with symptoms such as rigidity, resting tremor, bradykinesia, and postural instability (Tuite and Krawczewski, 2007).

The neuropathology of PD includes loss of dopaminergic neurons and the presence of LBs in the SN of the midbrain. LBs are an eosinophilic inclusion within the neuronal cytoplasm. The major component of LBs is α -synuclein in the form of amyloid fibrils. However, LBs also contain numerous other proteins and vesicular components (Shults, 2006; Wakabayashi et al., 2007; Xia et al., 2008).

The α -synuclein protein is encoded by the *SNCA* gene and is highly expressed in neurons, with the majority existing in presynaptic terminals. Mutations in *SNCA*, including missense, duplication, and triplication mutations, are linked to autosomal dominant familial PD (Farrer, 2006). α -Synuclein binds lipids, such as those in the plasma membrane and synaptic vesicles (Auluck et al., 2010). Under pathological conditions, α -synuclein aggregates to form insoluble amyloid fibrils via various forms of oligomeric intermediates (Lansbury and Lashuel, 2006). Binding of α -synuclein to lipids seems to modulate its tendency to produce these aggregates (Perrin et al., 2000).

PD is not the only disease characterized by α -synuclein aggregates. There is a group of neurodegenerative disorders that have abnormal deposition of intracellular α -synuclein aggregates as a common pathological characteristic. This group of diseases is referred to as synucleinopathies, which include PD, dementia with Lewy bodies (DLB), Lewy body-variant Alzheimer's disease, multiple

system atrophy (MSA), and neurodegeneration with brain iron accumulation (Galvin et al., 2001).

GBA1 mutations in Parkinson's disease

In a study involving 16 centers in 12 countries, mutations were screened in the *GBA1* coding regions in 5691 patients with PD and in 4898 controls. It showed *GBA1* mutations in 6.9% of patients with PD, whereas it only appeared in 1.3% of the control group (Sidransky et al., 2009). In other words, *GBA1* mutations are five times more likely to occur in patients with PD than in controls. Additionally, *GBA1* mutation frequency may differ by ethnicity. Ashkenazi Jews have *GBA1* mutation frequencies from 1/12 to 1/16, and the N370S variant is the most frequent allele, representing 70% of the mutant alleles (Sidransky et al., 2009). In contrast, other ethnic groups have a *GBA1* mutation frequency <1% (Sidransky et al., 2009). *GBA1* mutation frequency in Ashkenazi Jews further increases in patients with PD, ranging from 10.7% to 31.3%, whereas that of non-Ashkenazi Jewish patients with PD ranges from 2.3% to 9.4% (Sidransky and Lopez, 2012). These findings indicate that *GBA1* mutations might increase the incidence of PD. Other studies have supported the relationship between *GBA1* mutations and PD; that is, close relatives of patients with GD have an approximate 25% incidence rate of PD (Goker-Alpan et al., 2004; Halperin et al., 2006). Furthermore, the frequency of *GBA1* mutations in individuals with Parkinsonism is higher than that of mutations in other PD genes, such as α -synuclein and Parkin (Lwin et al., 2004).

Some distinctive clinical characteristics are associated with *GBA1*-linked PD. For example, the average age of initial diagnosis for *GBA1* mutation carriers is 4 years younger than that of non-carriers (Aharon-Peretz et al., 2004; Clark et al., 2007; Neumann et al., 2009). Moreover, more cognitive impairment, and less resting tremor and bradykinesia are reported in the PD of *GBA1* mutation carriers (Goker-Alpan et al., 2008; Sidransky et al., 2009).

The role of *GBA1* mutations in other synucleinopathies has also been explored. *GBA1* mutations were found in 3.5% (2/57) of patients with DLB, as opposed to 0.4% (2/554) of controls (Mata et al., 2008). Another study showed that *GBA1* mutations were found in 6% of 50 patients with DLB, whereas they were found in only 1% of 99 controls (Farrer et al., 2009). Not all synucleinopathies are associated with *GBA1* mutations. In a study in which all *GBA1* exons were examined from 75 brains with synucleinopathies (28 PD, 35 DLB, and 12 MSA), *GBA1* mutations

were found in 23% of DLB and 4% of PD brains, whereas none of the MSA subjects showed a *GBA1* mutation (Goker-Alpan et al., 2006). Another study independently examined *GBA1* mutations in the brains of 108 patients with MSA and 257 controls and failed to identify significant differences between the groups ($p=0.66$) (Segarane et al., 2009). In yet another study where N370S and L444P mutations were screened in 66 patients with MSA, no mutation carrier was detected (Jamrozik et al., 2010). Therefore, *GBA1* mutations may not be a general risk factor for synucleinopathies, but may selectively influence Lewy body diseases (LBDs), such as PD and DLB.

It has also been assessed whether *GBA1* mutations have effects on other neurodegenerative diseases, such as tauopathy. *GBA1* mutations were found in 28% of patients with DLB, 10% of patients with Alzheimer's disease (AD), and 3% of controls ($p<0.001$) (Clark et al., 2009). Although *GBA1* mutation frequency in patients with AD is lower than that in patients with LBDs, it is still higher than in control individuals. Therefore, *GBA1* mutations may contribute to the incidence of neurodegenerative diseases other than LBD. However, although *GBA1* mutation status was not determined, a decrease in GCCase activity is only detected in the cerebrospinal fluid of patients with PD (Balducci et al., 2007) and DLB (Parnetti et al., 2009), whereas such a reduction is not observed in patients with AD or frontotemporal dementia (Parnetti et al., 2009). Furthermore, the enzyme activity and protein levels of GCCase were reduced in many brain regions of PD patients carrying heterozygous *GBA1* mutations and sporadic PD patients (Gegg et al., 2012). Neuropathological examinations showed that demented subjects with LB-type pathologic changes were more likely to carry *GBA1* mutations than those with AD-type pathologic changes, which showed no difference to control individuals (Tsuang et al., 2012). The frequency of *GBA1* mutation in subjects with mixed pathology of LB-type and AD-type was in between that of pure LB and pure AD subjects, suggesting a strong association between *GBA1* mutation and LB-type neuropathological changes. Another study suggested that *GBA1* mutation status might be an independent risk factor for cognitive impairment in patients with PD (Alcalay et al., 2012) (also see below for the relationship between *GBA1* mutation and LB pathology).

***GBA1* mutations and Lewy body pathology**

GBA1 mutations have also been investigated in the context of neuropathological changes in various

neurodegenerative conditions, and a strong association has been found between *GBA1* mutations and LB pathology. Some of the mutant GCCase proteins are structurally unstable (Sawkar et al., 2006; Lieberman et al., 2007; Bendikov-Bar et al., 2011), and this may directly affect α -synuclein aggregation. In a study of brain samples from patients with PD and DLB, samples with a homozygous *GBA1* mutation showed that >80% of the LBs were co-localized with GCCase, and those with a heterozygous *GBA1* mutation showed a 75% GCCase co-localization rate (range, 32–90%) with LBs, compared to a mean of 4% in patients with PD and DLB without a *GBA1* mutation (Goker-Alpan et al., 2010). In addition, patients with GD and GD carriers with Parkinsonism have LB pathology (Clark et al., 2009). *GBA1* mutation carriers tend to have more cortical LBs (82%) than those of non-carriers (43%; $p<0.001$) (Clark et al., 2009). This finding suggests that Parkinsonism-associated GCCase mutants may promote α -synuclein aggregation directly, and have active roles in LB formation. However, because the pattern of GCCase co-localization with LBs is diverse among *GBA1* heterozygotes (Goker-Alpan et al., 2010), GCCase mutants may indirectly influence LB pathology, perhaps by sensitizing neurons to mitochondrial damage, environmental insults, and aging.

Additionally, Cullen et al. (2011) showed that when wild type or mutant *GBA1* is co-expressed with α -synuclein in MES23.5, PC12, and HEK293 cell lines, α -synuclein accumulation increased only in the mutant *GBA1* cell lines, but not in the wild type. In another study, accumulation of α -synuclein increased in cultured cells and the SN of mice following treatment with conduritol B epoxide, a GCCase inhibitor (Manning-Bog et al., 2009). These results led to the speculation that loss of GCCase function may cause α -synuclein accumulation. However, this speculation is probably an over-simplified view, because conflicting results exist. For example, treatment of the model used by Cullen et al. (2011) with conduritol B epoxide does not increase α -synuclein protein levels.

Potential mechanisms underlying the role of *GBA1* mutations in synucleinopathies

The role of *GBA1* mutations in the pathogenesis of PD and other LBDs is not fully understood. Homozygous *GBA1* mutants have deficient GCCase activity and cause the formation of Gaucher cells, which are mononuclear phagocytes with abnormal lipid accumulation. However, heterozygous

GBA1 mutants have varying degrees of enzyme activity ranging from 50% to normal levels and do not accumulate lipids (Lwin et al., 2004; Goker-Alpan et al., 2010). Furthermore, the link between deposition of the GCCase substrate and clinical signs of GD has been questioned. Based on the current understanding of GCCase biology, the effects of *GBA1* mutations on α -synuclein metabolism and aggregation can be explained by both gain-of-function and loss-of-function mechanisms. Below, we discuss the potential mechanisms by which *GBA1* mutations affect α -synuclein aggregation and disease (Figure 1).

Defects in lysosomal function and autophagy

Many of the major neurodegenerative diseases such as AD, PD, and Huntington's disease are the result of defects in the lysosome-autophagy pathway (Bahr and Bendiske, 2002; Menzies et al., 2006). Lysosomes are digestive organelles that decompose proteins, lipids, and organelles. Abnormal intracellular protein accumulation appears in both PD and GD, and it may influence disease severity. The mechanism of how mutant GCCase causes lysosomal dysfunction is unclear.

Human dopaminergic BE-M17 neuroblastoma cells show a decrease in the number of lysosomes, an increase

in cell death, and autophagosome accumulation in a dose-dependent manner when treated with the dopaminergic neurotoxin 1-methyl-4-phenylpyridine (Dehay et al., 2010). In addition, 1-methyl-4-phenylpyridine-treated cells show enhanced lysosomal membrane permeability, thereby causing release of soluble lysosomal components such as cathepsin D from lysosomes into the cytosol (Dehay et al., 2010). In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model and postmortem SN of patients with PD, neurons exhibit depleted lysosomes and accumulation of autophagosomes (Dehay et al., 2010). Similar results have been reported in a mouse model of neuropathic GD, which has a GCCase deficiency limited to neural and glial progenitor cells (Vitner et al., 2010). That study showed changes in cathepsin distribution and elevation of its activity and protein levels. Neuronal loss, astrogliosis, and microgliosis were observed in areas where cathepsin D was elevated, and these areas are known to be affected by the disease (Vitner et al., 2010). Cathepsin B and D protein levels also increase in other sphingolipidoses models such as Sandhoff, GM1 gangliosidosis, and Niemann-Pick A (Vitner et al., 2010). Therefore, these results suggest that lysosomal dysfunction is a common feature of PD and GD, and that *GBA1* mutations might contribute to these lysosomal abnormalities.

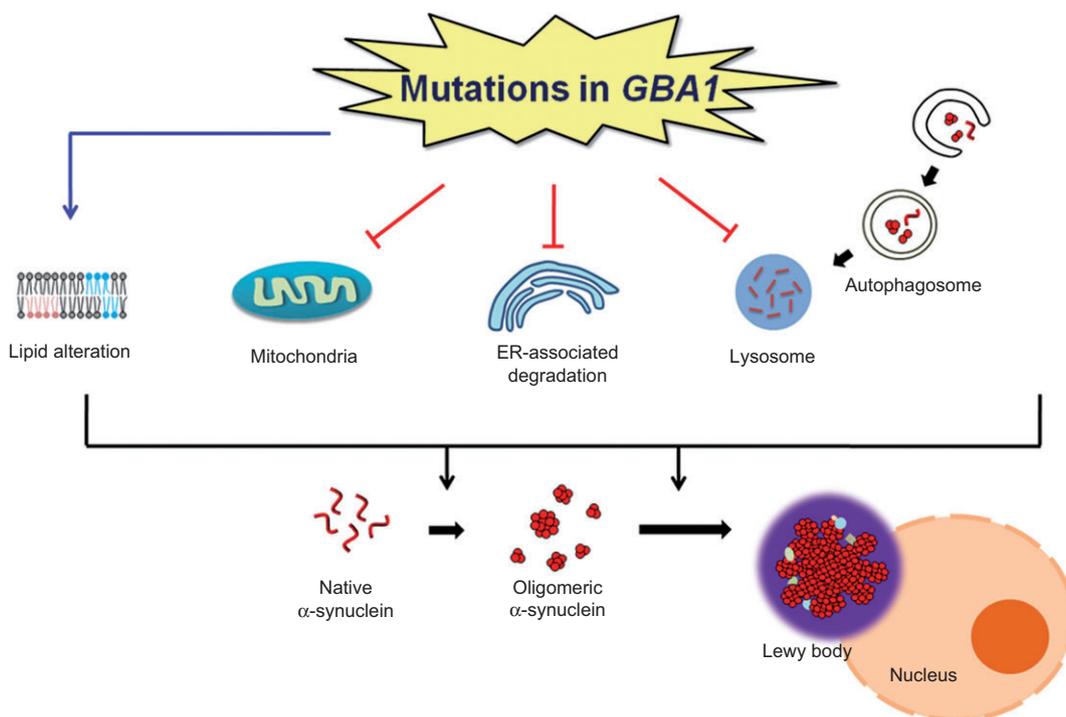


Figure 1 Potential mechanisms whereby *GBA1* mutations promote α -synuclein aggregation.

GBA1 mutations may affect autophagic-lysosomal functions, ERAD, mitochondrial functions, and membrane lipid compositions, thereby creating a cytoplasmic environment in favor of abnormal metabolism, misfolding, and/or oligomerization of α -synuclein.

Lysosomes are a critical component for all forms of autophagy, including macroautophagy, microautophagy, and chaperone-mediated autophagy. Autophagy-mediated clearance of damaged proteins is particularly important for neuronal survival. Several studies have shown that autophagy is responsible for degradation of α -synuclein aggregates (Lee et al., 2004; Sarkar et al., 2007), and impaired autophagy is observed in patients with PD and lysosomal storage diseases (Pan et al., 2008; Settembre et al., 2008). α -Synuclein accumulation by mutant GCase in cell models is ameliorated by rapamycin-induced autophagy in a dose- and time-dependent manner (Cullen et al., 2011), implicating the role of *GBA1* mutations in autophagic dysfunction. However, LC3 and beclin-1, markers of macroautophagy, do not change following starvation of fibroblasts from patients with GD (Pacheco et al., 2007). LAMP-2 and p62 accumulate in the thalamus, brain stem, and basal ganglia in a mouse model of neuropathic GD, which has a saposin C (an activator of GCase) deficiency and is homozygous for the *GBA1* V394L mutation, suggesting impaired macroautophagy (Sun et al., 2010). Additionally, overexpression of *GBA1* mutant

D409V in a PC12 cell model results in α -synuclein accumulation, which is rescued by rapamycin (Cullen et al., 2011). Therefore, *GBA1* mutations may cause defects in autophagy, thereby affecting α -synuclein metabolism (Figure 1).

GBA1 mutations may have very important implications in spreading Lewy pathology through lysosomal dysfunction (Figure 2). Neuronal LBs spread to a larger brain area as PD progresses (Braak and Del Tredici, 2008). Synucleinopathy lesions are also found in glial cells, such as astrocytes (in PD and DLB) and oligodendrocytes (in MSA). Neither of these glial cells expresses significant amounts of α -synuclein, raising the possibility of transfer of α -synuclein aggregates from neurons to glia. Based on this idea, oligodendrocyte-dominant α -synuclein accumulation in MSA may be explained by impaired clearance of transferred α -synuclein originating from neurons. Recently, direct cell-to-cell α -synuclein transmission has been experimentally demonstrated. α -Synuclein aggregates are transmitted through exocytosis and subsequent endocytosis between neighboring cells (Desplats et al., 2009; Danzer et al., 2011; Hansen et al.,

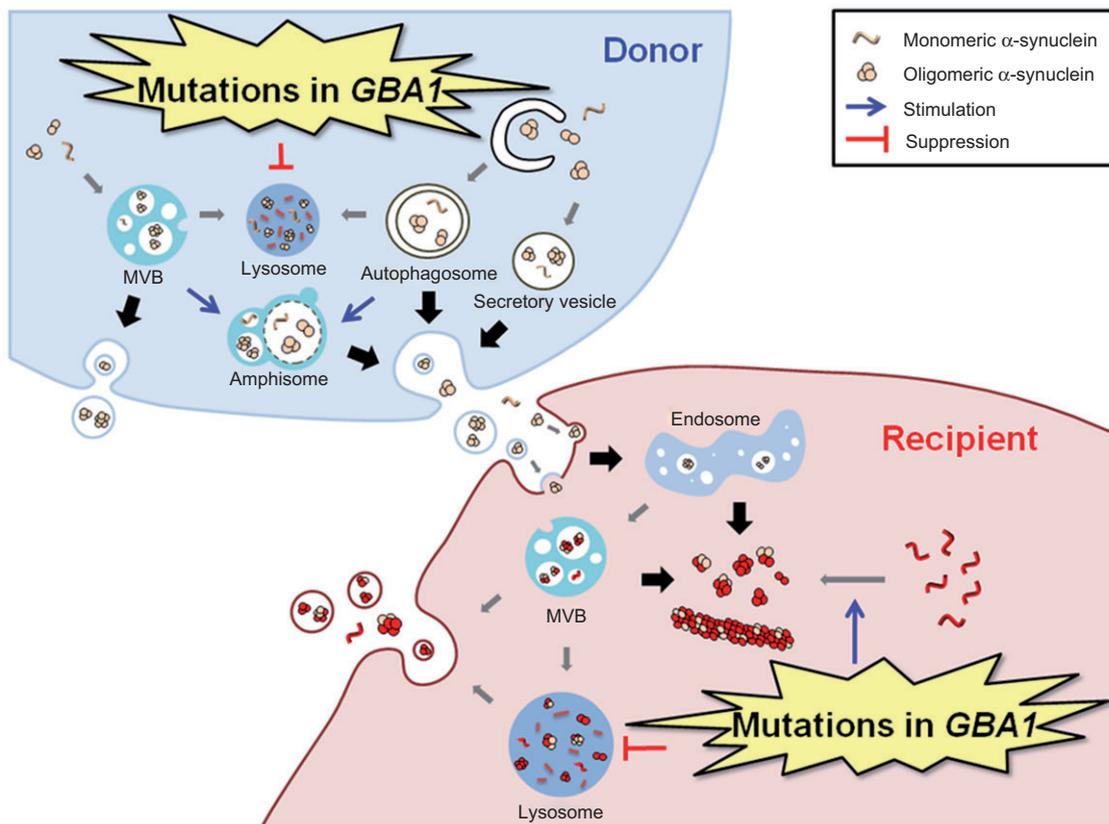


Figure 2 Hypothetical model explaining how *GBA1* mutations might promote transcellular transmission of α -synuclein aggregates. Various potential pathways for exocytosis of α -synuclein from donor cell and trafficking of internalized α -synuclein in recipient cells are illustrated. See text for details. MVB, multivesicular body.

2011; Volpicelli-Daley et al., 2011). Neuronal α -synuclein aggregates can be transferred to and accumulate in astrocytes (Lee et al., 2010). In cell-to-cell transmission of α -synuclein, *GBA1* mutations might exert their effects in both donor and recipient cells (Figure 2). In donor cells, *GBA1* mutations may reduce lysosomal function, shunting the trafficking pathways of multivesicular bodies and autophagosomes to the plasma membrane for exocytosis and also to each other for the formation of amphisomes, which then travel to the plasma membrane for exocytosis. These processes would result in exosome-associated α -synuclein. Lysosomal dysfunction may reduce overall α -synuclein catabolism and result in an increase in the translocation of this protein to secretory vesicles, whose identity is unknown. Exocytosis of these vesicles would generate vesicle-free extracellular α -synuclein. Previous studies have shown that α -synuclein is secreted via unconventional exocytosis (Lee et al., 2005; Jang et al., 2010), and exosome-associated release has also been suggested (Emmanouilidou et al., 2010; Alvarez-Erviti et al., 2011; Danzer et al., 2012). In recipient cells, internalization of extracellular α -synuclein aggregates may occur through endocytosis of the free protein or through direct fusion of exosomes to the plasma membrane. The transferred α -synuclein is thought to move through the endolysosomal pathway and to be degraded in lysosomes (Lee et al., 2008). However, under conditions of compromised lysosomal function, the transferred α -synuclein accumulates and leads to the formation of Lewy-like inclusions in cell models (Desplats et al., 2009). This transcellular α -synuclein transmission may ultimately lead to neuronal death (Desplats et al., 2009; Volpicelli-Daley et al., 2011). Partial breakdown of internalized aggregates may also increase the number of ‘seeds’ for α -synuclein aggregation and lead to increased release of recycled and newly-assembled α -synuclein aggregates. Whether *GBA1* mutations play a role in these α -synuclein transmission steps is an important question that should be addressed in future studies.

Endoplasmic reticulum-associated protein degradation and the ubiquitin proteasome system

The endoplasmic reticulum (ER) maintains protein folding homeostasis with its own quality control system. If misfolded proteins are detected in the ER, the proteins cannot move from the ER to the Golgi apparatus. Some of these proteins are ultimately destined to be degraded by being translocated to the cytosol through the Sec 61

ER membrane translocator (Scott and Schekman, 2008) or other ER proteins, such as derlin-1 (Lilley and Ploegh, 2004; Ye et al., 2004). The misfolded proteins are ubiquitinated in the cytosol and degraded by proteasomes (Ciechanover and Brundin, 2003). This process is referred to as endoplasmic reticulum-associated protein degradation (ERAD).

Several studies have been carried out to determine the relation between ERAD and GD, also ERAD and PD. Some of these studies show that mutant GCase is degraded via ERAD in the fibroblasts of patients with GD (Ron and Horowitz, 2005; Bendikov-Bar et al., 2011). Furthermore, the E3 ubiquitin ligase Parkin, which is implicated in autosomal-recessive juvenile PD, interacts with misfolded GCase, whereas wild-type GCase does not interact with Parkin (Horowitz and Ron, 2009). ER retention of mutant GCase promotes Parkin-dependent ERAD of this mutant protein. Furthermore, when proteasomes are pharmacologically inhibited, Parkin stimulates accumulation of GCase in aggresome-like structures. Considering these results, it is tempting to speculate that expression of *GBA1* mutations may delay degradation of natural Parkin substrates, resulting in accumulation of these substrates. This may lead to overload of the ubiquitin-proteasome system, disturbing global cytoplasmic proteostasis, and affect α -synuclein metabolism and formation of inclusion bodies (Figure 1).

Lipid alterations and accumulation

Alterations in membrane lipid composition are thought to be an important factor affecting the interaction between α -synuclein and lipid membranes (Kubo et al., 2005). Changes in lipid composition may occur through oxidative modifications or metabolic alterations (O'Donnell et al., 1999; Mosca et al., 2011). Significant alterations in membrane lipid composition, such as sphingolipidoses, have been reported in lysosomal storage diseases (Walkley, 2004). Thus, GCase dysfunction may lead to changes in membrane sphingolipid composition, interfere with α -synuclein binding to the membrane surface, and stimulate aggregation of α -synuclein in the cytoplasm (Figure 1). A recent study demonstrated that GC directly promotes oligomerization of α -synuclein (Mazzulli et al., 2011). In addition, lysosomal dysfunction and accumulation of GC and α -synuclein were observed in primary neurons deficient in GCase and in induced pluripotent stem cells derived from the fibroblasts of a patient with GD (Mazzulli et al., 2011). These models show α -synuclein-mediated neurotoxicity, and increased levels of α -synuclein inhibit intracellular GCase trafficking. As a result, GCase activity

decreases and GC accumulates. Therefore, these results suggest a positive feedback loop between α -synuclein accumulation and GCase abnormalities. In contrast, another series of *in vitro* studies showed that binding of gangliosides inhibits the aggregation of α -synuclein (Martinez et al., 2007; Wei et al., 2009). Therefore, the effects of the direct binding of glycosphingolipids on α -synuclein aggregation remain controversial.

GS levels were examined in the brains of 13 patients with GD (one type 1, eight type 2, and four type 3) and showed that the brains of patients with type 1 have normal levels (1.0 ng/mg) of GS, but that patients with type 2 have 24–437 ng/mg, and patients with type 3 have 14–32 ng/mg (Orvisky et al., 2002). However, *GBA1* mutations may not only affect GC and GS substrates but also cause global changes in cellular lipid composition. GC increases 12 times in THP-1 macrophages treated with conduritol B epoxide compared to that in control macrophages (Hein et al., 2007). A subcellular fractionation study in the same cell model showed that GC is distributed in all subcellular compartments, with lysosomes being the largest pool for this lipid (Hein et al., 2007). The amounts of other lipids increase, including ceramide, dihexosylceramide, trihexosylceramide, and phosphatidylglycerol (Hein et al., 2007, 2008). These changes in glycosphingolipids may particularly affect lipid raft function by interfering with the sorting and trafficking of proteins and lipids associated with the rafts. Notably, α -synuclein is localized in some of the lipid rafts in neuronal cells (Fortin et al., 2004; Kubo et al., 2005). Therefore, it is speculated that *GBA1* mutation-induced lipid changes may alter the interaction between lipid microdomains and α -synuclein.

Another hypothesis is that alterations in ceramide metabolism regulate LB formation. Ceramide is a GCase product, and a genetic-association study has suggested that several genes related to ceramide metabolism are associated with LB pathology (Bras et al., 2008). Furthermore, inclusion of α -synuclein in *Caenorhabditis elegans* increases by 35% due to deletion of the *Lagr-1* gene, a ceramide synthase homologue (van Ham et al., 2008). As the loss-of-function *GBA1* mutations would not produce ceramide, *Lagr-1* deletion phenotypes may reflect the pathogenic roles of loss-of-function *GBA1* mutations.

Physical interaction between GCase and α -synuclein was demonstrated in acidic conditions, which mimicked the lysosomal lumen (Yap et al., 2011), and further investigation by the same group showed that membrane-bound α -synuclein interacted with GCase and inhibited the enzyme activity (Yap et al., 2013). Magnetic resonance spectroscopic imaging study with PD patients with heterozygous *GBA1* mutations showed neurodegeneration in the putamen and

the midbrain, and this seemed to be associated with alterations of phospholipid metabolism (Brockmann et al., 2012). Altered function or abnormal aggregation of α -synuclein might explain these pathological changes.

Mitochondrial dysfunction

Mitochondrial defects are associated with several neurodegenerative diseases, and have been reported in some lysosomal storage disorders. For example, mitochondrial cytochrome C oxidase activity decreases in a mouse model of GM1 gangliosidosis, and mitochondrial membrane potential and morphology changed subsequently (Tamura et al., 2008). A mouse model of GM2 gangliosidosis also showed an abnormality in the number of mitochondria and fission (Jeyakumar et al., 2009). The role of *GBA1* mutations in mitochondrial function has not been studied extensively. However, given the relationship between lysosomal and mitochondrial functions, as well as the effects of mitochondrial deficiency on α -synuclein aggregation, the role of mitochondria in *GBA1* mutation-induced α -synuclein pathology is of potential importance (Figure 1).

Conclusions and outstanding questions

Genetic and pathological studies suggest that *GBA1* mutations are implicated in LBDs, such as PD and DLB, ranking them as one of the most important genetic risk factors for these diseases. *GBA1* mutations might also be associated with other neurodegenerative diseases such as AD, but the evidence is sparse and weak compared to that for LBDs. Both gain-of-function and loss-of-function mechanisms have been suggested as ways in which *GBA1* mutations act during the disease process. Specifically, lysosomal-autophagic dysfunction, defects in ERAD, and alterations in membrane lipid composition have been proposed as mechanisms by which *GBA1* mutations cause LBDs and α -synuclein accumulation. Adeno-associated virus (AAV)-mediated expression of GCase reversed the abnormal accumulation of glucosylsphingosine and reduced the levels of proteinase K-resistant α -synuclein in symptomatic *GBA1* (D409V/D409V) mice (Sardi et al., 2013). Furthermore, overexpression of GCase in A53T α -synuclein mice reduced the levels of soluble α -synuclein. These studies suggest that enhancing GCase activity is a potential therapeutic strategy for synucleinopathies with or without *GBA1* mutations.

Although the link between *GBA1* mutations and LBDs is a breakthrough in the field of LBD pathobiology, several critical questions remain. Why are the synucleinopathies most closely associated with *GBA1* mutations among neurodegenerative diseases? Why is MSA not associated with *GBA1* mutations even though it is a synucleinopathy? Which cellular alterations caused by *GBA1* mutations are the most critical and relevant to LBDs and, particularly, to α -synuclein aggregation? How do *GBA1* mutations influence transcellular α -synuclein transmission? It is likely that we will enter a novel aspect of disease mechanisms

by addressing these questions, which might provide insights into developing new therapies for LBDs.

Acknowledgements: This work was supported by the National Research Foundation grant funded by the Korean Government (MEST) (No. 2010-0015188), and the Korea Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (A111228).

Received November 13, 2012; accepted February 15, 2013; previously published online February 21, 2013

References

- Aharon-Peretz, J., Rosenbaum, H., and Gershoni-Baruch, R. (2004). Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. *N. Engl. J. Med.* *351*, 1972–1977.
- Alcalay, R.N., Caccappolo, E., Mejia-Santana, H., Tang, M., Rosado, L., Orbe Reilly, M., Ruiz, D., Ross, B., Verbitsky, M., Kisselev, S., et al. (2012). Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. *Neurology* *78*, 1434–1440.
- Alonso-Canovas, A., Katschnig, P., Tucci, A., Carecchio, M., Wood, N.W., Edwards, M., Martinez Castrillo, J.C., Burke, D., Heales, S., and Bhatia, K.P. (2010). Atypical parkinsonism with apraxia and supranuclear gaze abnormalities in type 1 Gaucher disease. Expanding the spectrum: case report and literature review. *Mov. Disord.* *25*, 1506–1509.
- Alvarez-Erviti, L., Seow, Y., Schapira, A.H., Gardiner, C., Sargent, I.L., Wood, M.J., and Cooper, J.M. (2011). Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission. *Neurobiol. Dis.* *42*, 360–367.
- Auluck, P.K., Caraveo, G., and Lindquist, S. (2010). alpha-Synuclein: membrane interactions and toxicity in Parkinson's disease. *Annu. Rev. Cell Dev. Biol.* *26*, 211–233.
- Bahr, B.A. and Bendiske, J. (2002). The neuropathogenic contributions of lysosomal dysfunction. *J. Neurochem.* *83*, 481–489.
- Balducci, C., Pierguidi, L., Persichetti, E., Parnetti, L., Sbaragli, M., Tassi, C., Orlacchio, A., Calabresi, P., Beccari, T., and Rossi, A. (2007). Lysosomal hydrolases in cerebrospinal fluid from subjects with Parkinson's disease. *Mov. Disord.* *22*, 1481–1484.
- Bendikov-Bar, I., Ron, I., Filocamo, M., and Horowitz, M. (2011). Characterization of the ERAD process of the L444P mutant glucocerebrosidase variant. *Blood Cells Mol. Dis.* *46*, 4–10.
- Biegstraaten, M., van Schaik, I.N., Aerts, J.M., and Hollak, C.E. (2008). 'Non-neuronopathic' Gaucher disease reconsidered. Prevalence of neurological manifestations in a Dutch cohort of type I Gaucher disease patients and a systematic review of the literature. *J. Inher. Metab. Dis.* *31*, 337–349.
- Biegstraaten, M., van Schaik, I.N., Aerts, J.M., Langeveld, M., Mannens, M.M., Bour, L.J., Sidransky, E., Tayebi, N., Fitzgibbon, E., and Hollak, C.E. (2011). A monozygotic twin pair with highly discordant Gaucher phenotypes. *Blood Cells Mol. Dis.* *46*, 39–41.
- Braak, H. and Del Tredici, K. (2008). Invited Article: Nervous system pathology in sporadic Parkinson disease. *Neurology* *70*, 1916–1925.
- Bras, J., Singleton, A., Cookson, M.R., and Hardy, J. (2008). Emerging pathways in genetic Parkinson's disease: potential role of ceramide metabolism in Lewy body disease. *FEBS J.* *275*, 5767–5773.
- Brockmann, K., Hilker, R., Pilatus, U., Baudrexel, S., Sruilijes, K., Magerkurth, J., Hauser, A.K., Schulte, C., Csoti, I., Merten, C.D., et al. (2012). GBA-associated PD. Neurodegeneration, altered membrane metabolism, and lack of energy failure. *Neurology* *79*, 213–220.
- Capablo, J.L., Saenz de Cabezón, A., Fraile, J., Alfonso, P., Pócovi, M., and Giraldo, P. (2008). Neurological evaluation of patients with Gaucher disease diagnosed as type 1. *J. Neurol. Neurosurg. Psychiatry* *79*, 219–222.
- Ciechanover, A. and Brundin, P. (2003). [The ubiquitin proteasome system in neurodegenerative diseases: sometimes the chicken, sometimes the egg.](#) *Neuron* *40*, 427–446.
- Clark, L.N., Ross, B.M., Wang, Y., Mejia-Santana, H., Harris, J., Louis, E.D., Cote, L.J., Andrews, H., Fahn, S., Waters, C., et al. (2007). Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. *Neurology* *69*, 1270–1277.
- Clark, L.N., Kartsaklis, L.A., Wolf Gilbert, R., Dorado, B., Ross, B.M., Kisselev, S., Verbitsky, M., Mejia-Santana, H., Cote, L.J., Andrews, H., et al. (2009). [Association of glucocerebrosidase mutations with dementia with lewy bodies.](#) *Arch. Neurol.* *66*, 578–583.
- Cullen, V., Sardi, S.P., Ng, J., Xu, Y.H., Sun, Y., Tomlinson, J.J., Kolodziej, P., Kahn, I., Saftig, P., Woulfe, J., et al. (2011). Acid beta-glucosidase mutants linked to Gaucher disease, Parkinson disease, and Lewy body dementia alter alpha-synuclein processing. *Ann. Neurol.* *69*, 940–953.
- Danzer, K.M., Ruf, W.P., Putcha, P., Joyner, D., Hashimoto, T., Glabe, C., Hyman, B.T., and McLean, P.J. (2011). Heat-shock protein 70 modulates toxic extracellular alpha-synuclein oligomers and rescues trans-synaptic toxicity. *FASEB J.* *25*, 326–336.
- Danzer, K.M., Kranich, L.R., Ruf, W.P., Cagsal-Getkin, O., Winslow, A.R., Zhu, L., Vanderburg, C.R., and McLean, P.J. (2012). Exosomal cell-to-cell transmission of alpha-synuclein oligomers. *Mol. Neurodegener.* *7*, 42.
- de Rijk, M.C., Launer, L.J., Berger, K., Breteler, M.M., Dartigues, J.F., Baldereschi, M., Fratiglioni, L., Lobo, A., Martinez-Lage, J.,

- Trenkwalder, C., et al. (2000). Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. *Neurologic Diseases in the Elderly Research Group. Neurology* 54, S21–23.
- Dehay, B., Bove, J., Rodriguez-Muela, N., Perier, C., Recasens, A., Boya, P., and Vila, M. (2010). Pathogenic lysosomal depletion in Parkinson's disease. *J. Neurosci.* 30, 12535–12544.
- Desplats, P., Lee, H.J., Bae, E.J., Patrick, C., Rockenstein, E., Crews, L., Spencer, B., Masliah, E., and Lee, S.J. (2009). [Inclusion formation and neuronal cell death through neuron-to-neuron transmission of \$\alpha\$ -synuclein.](#) *Proc. Natl. Acad. Sci. USA* 106, 13010–13015.
- Emmanouilidou, E., Melachroinou, K., Roumeliotis, T., Garbis, S.D., Ntzouni, M., Margaritis, L.H., Stefanis, L., and Vekrellis, K. (2010). [Cell-produced \$\alpha\$ -synuclein is secreted in a calcium-dependent manner by exosomes and impacts neuronal survival.](#) *J. Neurosci.* 30, 6838–6851.
- Farrer, M.J. (2006). [Genetics of Parkinson disease: paradigm shifts and future prospects.](#) *Nat. Rev. Genet.* 7, 306–318.
- Farrer, M.J., Williams, L.N., Algom, A.A., Kachergus, J., Hulihan, M.M., Ross, O.A., Rajput, A., Papapetropoulos, S., Mash, D.C., and Dickson, D.W. (2009). [Glucosidase- \$\beta\$ variations and Lewy body disorders.](#) *Parkinsonism Relat. Disord.* 15, 414–416.
- Fortin, D.L., Troyer, M.D., Nakamura, K., Kubo, S., Anthony, M.D., and Edwards, R.H. (2004). [Lipid rafts mediate the synaptic localization of \$\alpha\$ -synuclein.](#) *J. Neurosci.* 24, 6715–6723.
- Futerman, A.H., Sussman, J.L., Horowitz, M., Silman, I., and Zimran, A. (2004). [New directions in the treatment of Gaucher disease.](#) *Trends Pharmacol. Sci.* 25, 147–151.
- Galvin, J.E., Lee, V.M., and Trojanowski, J.Q. (2001). [Synucleinopathies: clinical and pathological implications.](#) *Arch. Neurol.* 58, 186–190.
- Gegg, M.E., Burke, D., Heales, S.J., Cooper, J.M., Hardy, J., Wood, N.W., and Schapira, A.H. (2012). [Glucocerebrosidase deficiency in substantia nigra of Parkinson disease brains.](#) *Ann. Neurol.* 72, 455–463.
- Goker-Alpan, O., Stubblefield, B.K., Giasson, B.I., and Sidransky, E. (2010). [Glucocerebrosidase is present in \$\alpha\$ -synuclein inclusions in Lewy body disorders.](#) *Acta Neuropathol.* 120, 641–649.
- Goker-Alpan, O., Schiffmann, R., LaMarca, M.E., Nussbaum, R.L., McInerney-Leo, A., and Sidransky, E. (2004). [Parkinsonism among Gaucher disease carriers.](#) *J. Med. Genet.* 41, 937–940.
- Goker-Alpan, O., Lopez, G., Vithayathil, J., Davis, J., Hallett, M., and Sidransky, E. (2008). [The spectrum of parkinsonian manifestations associated with glucocerebrosidase mutations.](#) *Arch. Neurol.* 65, 1353–1357.
- Goker-Alpan, O., Hruska, K.S., Orvisky, E., Kishnani, P.S., Stubblefield, B.K., Schiffmann, R., and Sidransky, E. (2005). [Divergent phenotypes in Gaucher disease implicate the role of modifiers.](#) *J. Med. Genet.* 42, e37.
- Goker-Alpan, O., Giasson, B.I., Eblan, M.J., Nguyen, J., Hurtig, H.I., Lee, V.M., Trojanowski, J.Q., and Sidransky, E. (2006). [Glucocerebrosidase mutations are an important risk factor for Lewy body disorders.](#) *Neurology* 67, 908–910.
- Halperin, A., Elstein, D., and Zimran, A. (2006). [Increased incidence of Parkinson disease among relatives of patients with Gaucher disease.](#) *Blood Cells Mol. Dis.* 36, 426–428.
- Hansen, C., Angot, E., Bergstrom, A.L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Kallunki, P., Fog, K., et al. (2011). [\$\alpha\$ -Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells.](#) *J. Clin. Invest.* 121, 715–725.
- Hein, L.K., Meikle, P.J., Hopwood, J.J., and Fuller, M. (2007). [Secondary sphingolipid accumulation in a macrophage model of Gaucher disease.](#) *Mol. Genet. Metab.* 92, 336–345.
- Hein, L.K., Duplock, S., Hopwood, J.J., and Fuller, M. (2008). [Lipid composition of microdomains is altered in a cell model of Gaucher disease.](#) *J. Lipid. Res.* 49, 1725–1734.
- Horowitz, M. and Ron, I. (2009). [Interaction between parkin and glucocerebrosidase: a possible link between Parkinson disease and Gaucher disease.](#) *Mol. Genet. Metab.* 96, S27–S27.
- Hruska, K.S., LaMarca, M.E., Scott, C.R., and Sidransky, E. (2008). [Gaucher disease: mutation and polymorphism spectrum in the glucocerebrosidase gene \(GBA\).](#) *Hum. Mutat.* 29, 567–583.
- Jamrozik, Z., Lugowska, A., Slawek, J., and Kwiecinski, H. (2010). [Glucocerebrosidase mutations p.L444P and p.N370S are not associated with multisystem atrophy, progressive supranuclear palsy and corticobasal degeneration in Polish patients.](#) *J. Neurol.* 257, 459–460.
- Jang, A., Lee, H.J., Suk, J.E., Jung, J.W., Kim, K.P., and Lee, S.J. (2010). [Non-classical exocytosis of \$\alpha\$ -synuclein is sensitive to folding states and promoted under stress conditions.](#) *J. Neurochem.* 113, 1263–1274.
- Jeyakumar, M., Williams, I., Smith, D., Cox, T.M., and Platt, F.M. (2009). [Critical role of iron in the pathogenesis of the murine gangliosidoses.](#) *Neurobiol. Dis.* 34, 406–416.
- Jmoudiak, M. and Futerman, A.H. (2005). [Gaucher disease: pathological mechanisms and modern management.](#) *Br. J. Haematol.* 129, 178–188.
- Kubo, S., Nemani, V.M., Chalkley, R.J., Anthony, M.D., Hattori, N., Mizuno, Y., Edwards, R.H., and Fortin, D.L. (2005). [A combinatorial code for the interaction of \$\alpha\$ -synuclein with membranes.](#) *J. Biol. Chem.* 280, 31664–31672.
- Lansbury, P.T. and Lashuel, H.A. (2006). [A century-old debate on protein aggregation and neurodegeneration enters the clinic.](#) *Nature* 443, 774–779.
- Lee, H.J., Patel, S., and Lee, S.J. (2005). [Intravesicular localization and exocytosis of \$\alpha\$ -synuclein and its aggregates.](#) *J. Neurosci.* 25, 6016–6024.
- Lee, H.J., Khoshaghideh, F., Patel, S., and Lee, S.J. (2004). [Clearance of \$\alpha\$ -synuclein oligomeric intermediates via the lysosomal degradation pathway.](#) *J. Neurosci.* 24, 1888–1896.
- Lee, H.J., Suk, J.E., Bae, E.J., Lee, J.H., Paik, S.R., and Lee, S.J. (2008). [Assembly-dependent endocytosis and clearance of extracellular \$\alpha\$ -synuclein.](#) *Int. J. Biochem Cell Biol.* 40, 1835–1849.
- Lee, H.J., Suk, J.E., Patrick, C., Bae, E.J., Cho, J.H., Rho, S., Hwang, D., Masliah, E., and Lee, S.J. (2010). [Direct transfer of \$\alpha\$ -synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies.](#) *J. Biol. Chem.* 285, 9262–9272.
- Lieberman, R.L., Wustman, B.A., Huertas, P., Powe, A.C., Jr., Pine, C.W., Khanna, R., Schlossmacher, M.G., Ringe, D., and Petsko, G.A. (2007). [Structure of acid \$\beta\$ -glucosidase with pharmacological chaperone provides insight into Gaucher disease.](#) *Nat. Chem. Biol.* 3, 101–107.
- Lilley, B.N. and Ploegh, H.L. (2004). [A membrane protein required for dislocation of misfolded proteins from the ER.](#) *Nature* 429, 834–840.
- Lwin, A., Orvisky, E., Goker-Alpan, O., LaMarca, M.E., and Sidransky, E. (2004). [Glucocerebrosidase mutations in subjects with parkinsonism.](#) *Mol. Genet. Metab.* 81, 70–73.

- Manning-Bog, A.B., Schule, B., and Langston, J.W. (2009). α -Synuclein-glucocerebrosidase interactions in pharmacological Gaucher models: a biological link between Gaucher disease and parkinsonism. *Neurotoxicology* 30, 1127–1132.
- Martinez, Z., Zhu, M., Han, S., and Fink, A.L. (2007). GM1 specifically interacts with α -synuclein and inhibits fibrillation. *Biochemistry* 46, 1868–1877.
- Mata, I.F., Samii, A., Schneer, S.H., Roberts, J.W., Griffith, A., Leis, B.C., Schellenberg, G.D., Sidransky, E., Bird, T.D., Leverenz, J.B., et al. (2008). [Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders](#). *Arch. Neurol.* 65, 379–382.
- Mazzulli, J.R., Xu, Y.H., Sun, Y., Knight, A.L., McLean, P.J., Caldwell, G.A., Sidransky, E., Grabowski, G.A., and Krainc, D. (2011). Gaucher disease glucocerebrosidase and α -synuclein form a bidirectional pathogenic loop in synucleinopathies. *Cell* 146, 37–52.
- Menzies, F.M., Ravikumar, B., and Rubinsztein, D.C. (2006). [Protective roles for induction of autophagy in multiple proteinopathies](#). *Autophagy* 2, 224–225.
- Mosca, M., Ceglie, A., and Ambrosone, L. (2011). [Effect of membrane composition on lipid oxidation in liposomes](#). *Chem. Phys. Lipids* 164, 158–165.
- Neudorfer, O., Giladi, N., Elstein, D., Abrahamov, A., Turezkite, T., Aghai, E., Reches, A., Bembi, B., and Zimran, A. (1996). Occurrence of Parkinson's syndrome in type I Gaucher disease. *Q. J. Med.* 89, 691–694.
- Neumann, J., Bras, J., Deas, E., O'Sullivan, S.S., Parkkinen, L., Lachmann, R.H., Li, A., Holton, J., Guerreiro, R., Paudel, R., et al. (2009). Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. *Brain* 132, 1783–1794.
- O'Donnell, V.B., Eiserich, J.P., Chumley, P.H., Jablonsky, M.J., Krishna, N.R., Kirk, M., Barnes, S., Darley-Usmar, V.M., and Freeman, B.A. (1999). Nitration of unsaturated fatty acids by nitric oxide-derived reactive nitrogen species peroxynitrite, nitrous acid, nitrogen dioxide, and nitronium ion. *Chem. Res. Toxicol.* 12, 83–92.
- Orvisky, E., Park, J.K., LaMarca, M.E., Ginns, E.I., Martin, B.M., Tayebi, N., and Sidransky, E. (2002). [Glucosylsphingosine accumulation in tissues from patients with Gaucher disease: correlation with phenotype and genotype](#). *Mol. Genet. Metab.* 76, 262–270.
- Pacheco, C.D., Kunkel, R., and Lieberman, A.P. (2007). Autophagy in Niemann-Pick C disease is dependent upon Beclin-1 and responsive to lipid trafficking defects. *Hum. Mol. Genet.* 16, 1495–1503.
- Pan, T., Kondo, S., Le, W., and Jankovic, J. (2008). The role of autophagy-lysosome pathway in neurodegeneration associated with Parkinson's disease. *Brain* 131, 1969–1978.
- Parnetti, L., Balducci, C., Pierguidi, L., De Carlo, C., Peducci, M., D'Amore, C., Padiglioni, C., Mastrocola, S., Persichetti, E., Paciotti, S., et al. (2009). Cerebrospinal fluid beta-glucocerebrosidase activity is reduced in dementia with Lewy bodies. *Neurobiol. Dis.* 34, 484–486.
- Pastores, G.M. (1997). Gaucher's Disease. Pathological features. *Baillieres Clin. Haematol.* 10, 739–749.
- Pennelli, N., Scaravilli, F., and Zaccchello, F. (1969). The morphogenesis of Gaucher cells investigated by electron microscopy. *Blood* 34, 331–347.
- Perrin, R.J., Woods, W.S., Clayton, D.F., and George, J.M. (2000). Interaction of human α -synuclein and Parkinson's disease variants with phospholipids. Structural analysis using site-directed mutagenesis. *J. Biol. Chem.* 275, 34393–34398.
- Ron, I. and Horowitz, M. (2005). ER retention and degradation as the molecular basis underlying Gaucher disease heterogeneity. *Hum. Mol. Genet.* 14, 2387–2398.
- Sardi, S.P., Clarke, J., Viel, C., Chan, M., Tamsett, T.J., Treleaven, C.M., Bu, J., Sweet, L., Passini, M.A., Dodge, J.C., et al. (2013). Augmenting CNS glucocerebrosidase activity as a therapeutic strategy for parkinsonism and other Gaucher-related synucleinopathies. *Proc. Natl. Acad. Sci. USA* 110, 3537–3542.
- Sarkar, S., Perlstein, E.O., Imarisio, S., Pineau, S., Cordenier, A., Maglathlin, R.L., Webster, J.A., Lewis, T.A., O'Kane, C.J., Schreiber, S.L., et al. (2007). Small molecules enhance autophagy and reduce toxicity in Huntington's disease models. *Nat. Chem. Biol.* 3, 331–338.
- Sawkar, A.R., Schmitz, M., Zimmer, K.P., Reczek, D., Edmunds, T., Balch, W.E., and Kelly, J.W. (2006). Chemical chaperones and permissive temperatures alter localization of Gaucher disease associated glucocerebrosidase variants. *ACS Chem. Biol.* 1, 235–251.
- Scott, D.C. and Schekman, R. (2008). Role of Sec61p in the ER-associated degradation of short-lived transmembrane proteins. *J. Cell Biol.* 181, 1095–1105.
- Segarane, B., Li, A., Paudel, R., Scholz, S., Neumann, J., Lees, A., Revesz, T., Hardy, J., Mathias, C.J., Wood, N.W., et al. (2009). Glucocerebrosidase mutations in 108 neuropathologically confirmed cases of multiple system atrophy. *Neurology* 72, 1185–1186.
- Settembre, C., Fraldi, A., Jahreiss, L., Spampinato, C., Venturi, C., Medina, D., de Pablo, R., Tacchetti, C., Rubinsztein, D.C., and Ballabio, A. (2008). A block of autophagy in lysosomal storage disorders. *Hum. Mol. Genet.* 17, 119–129.
- Shults, C.W. (2006). Lewy bodies. *Proc. Natl. Acad. Sci. USA* 103, 1661–1668.
- Sidransky, E. and Lopez, G. (2012). [The link between the GBA gene and parkinsonism](#). *Lancet Neurol.* 11, 986–998.
- Sidransky, E., Nalls, M.A., Aasly, J.O., Aharon-Peretz, J., Annesi, G., Barbosa, E.R., Bar-Shira, A., Berg, D., Bras, J., Brice, A., et al. (2009). Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N. Engl. J. Med.* 361, 1651–1661.
- Sun, Y., Liou, B., Ran, H., Skelton, M.R., Williams, M.T., Vorhees, C.V., Kitatani, K., Hannun, Y.A., Witte, D.P., Xu, Y.H., et al. (2010). Neuronopathic Gaucher disease in the mouse: viable combined selective saposin C deficiency and mutant glucocerebrosidase (V394L) mice with glucosylsphingosine and glucosylceramide accumulation and progressive neurological deficits. *Hum. Mol. Genet.* 19, 1088–1097.
- Takamura, A., Higaki, K., Kajimaki, K., Otsuka, S., Ninomiya, H., Matsuda, J., Ohno, K., Suzuki, Y., and Nanba, E. (2008). Enhanced autophagy and mitochondrial aberrations in murine G_{M1} -gangliosidosis. *Biochem. Biophys. Res. Commun.* 367, 616–622.
- Tsuang, D., Leverenz, J.B., Lopez, O.L., Hamilton, R.L., Bennett, D.A., Schneider, J.A., Buchman, A.S., Larson, E.B., Crane, P.K., Kaye, J.A., et al. (2012). GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology. *Neurology* 79, 1944–1950.

- Tuite, P.J. and Krawczewski, K. (2007). Parkinsonism: a review-of-systems approach to diagnosis. *Semin. Neurol.* 27, 113–122.
- van Ham, T.J., Thijssen, K.L., Breitling, R., Hofstra, R.M., Plasterk, R.H., and Nollen, E.A. (2008). *C. elegans* model identifies genetic modifiers of α -synuclein inclusion formation during aging. *PLoS Genet.* 4, e1000027.
- Vitner, E.B., Dekel, H., Zigdon, H., Shachar, T., Farfel-Becker, T., Eilam, R., Karlsson, S., and Futerman, A.H. (2010). Altered expression and distribution of cathepsins in neuronopathic forms of Gaucher disease and in other sphingolipidoses. *Hum. Mol. Genet.* 19, 3583–3590.
- Volpicelli-Daley, L.A., Luk, K.C., Patel, T.P., Tanik, S.A., Riddle, D.M., Stieber, A., Meaney, D.F., Trojanowski, J.Q., and Lee, V.M. (2011). Exogenous α -synuclein fibrils induce Lewy body pathology leading to synaptic dysfunction and neuron death. *Neuron* 72, 57–71.
- Wakabayashi, K., Tanji, K., Mori, F., and Takahashi, H. (2007). The Lewy body in Parkinson's disease: molecules implicated in the formation and degradation of α -synuclein aggregates. *Neuropathology* 27, 494–506.
- Walkley, S.U. (2004). Secondary accumulation of gangliosides in lysosomal storage disorders. *Semin. Cell Dev. Biol.* 15, 433–444.
- Wei, J., Fujita, M., Nakai, M., Waragai, M., Sekigawa, A., Sugama, S., Takenouchi, T., Masliah, E., and Hashimoto, M. (2009). Protective role of endogenous gangliosides for lysosomal pathology in a cellular model of synucleinopathies. *Am. J. Pathol.* 174, 1891–1909.
- Wong, K., Sidransky, E., Verma, A., Mixon, T., Sandberg, G.D., Wakefield, L.K., Morrison, A., Lwin, A., Colegial, C., Allman, J.M., et al. (2004). Neuropathology provides clues to the pathophysiology of Gaucher disease. *Mol. Genet. Metab.* 82, 192–207.
- Xia, Q., Liao, L., Cheng, D., Duong, D.M., Gearing, M., Lah, J.J., Levey, A.I., and Peng, J. (2008). Proteomic identification of novel proteins associated with Lewy bodies. *Front Biosci.* 13, 3850–3856.
- Yap, T.L., Velayati, A., Sidransky, E., and Lee, J.C. (2013). Membrane-bound alpha-synuclein interacts with glucocerebrosidase and inhibits enzyme activity. *Mol. Genet. Metab.* 108, 56–64.
- Yap, T.L., Gruschus, J.M., Velayati, A., Westbroek, W., Goldin, E., Moaven, N., Sidransky, E., and Lee, J.C. (2011). Alpha-synuclein interacts with Glucocerebrosidase providing a molecular link between Parkinson and Gaucher diseases. *J. Biol. Chem.* 286, 28080–28088.
- Ye, Y., Shibata, Y., Yun, C., Ron, D., and Rapoport, T.A. (2004). A membrane protein complex mediates retro-translocation from the ER lumen into the cytosol. *Nature* 429, 841–847.



Na-Young Yang graduated college from Yonsei University, Wonju, Korea. She is a graduate student in Konkuk University, Seoul, Korea. She has been studying the effects of lysosomal dysfunction on α -synuclein metabolism in tissue culture models.



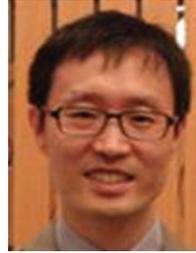
Yu-Na Lee was a student intern in Konkuk University and is currently attending St. Paul's School in Concord, New Hampshire.



Prof. He-Jin Lee did her undergraduate studies from POSTECH, Pohang, Korea. She then went to the US for her PhD studies in the Dept. of Biochemistry in Boston University School of Medicine. After graduation, she started her postdoctoral career at the Parkinson's Institute, Sunnyvale, CA and then moved to Konkuk University, Seoul, Korea, where she is now an Associate Professor. From her postdoctoral career to now, Prof. Lee has been studying the role of α -synuclein aggregation in the pathogenesis of Parkinson's disease. She had collaborated with Prof. Seung-Jae Lee to write high impact research and review papers.



Prof. Yoon Suk Kim received his PhD in Biomedical Laboratory Science from Yonsei University, Korea. He completed his postdoctoral training at the Parkinson's Institute and was a research Assistant Professor at Korea University. Prof. Kim is currently a full professor in the Department of Biomedical Laboratory Science, Yonsei University. His scientific interest lies in understanding the interaction of α -synuclein with biological membranes and lipid metabolism in cardiovascular and neurodegenerative diseases.



Prof. Seung-Jae Lee went to Seoul National University, Seoul, Korea, for his undergraduate studies and received PhD in molecular biology from POSTECH, Pohang, Korea. He then went to the US and conducted postdoctoral research at National Institutes of Health, Bethesda, MD and at Harvard Medical School, Boston, MA. Prof. Lee started his independent research career at the Parkinson's Institute, Sunnyvale, CA as an Assistant Professor, and then moved to Konkuk University, Seoul, Korea, where he is now a full Professor. Prof. Lee has been studying the role of protein aggregation in the pathogenesis of neurodegenerative diseases with particular interest in the pathophysiological function of α -synuclein in Lewy body diseases, including Parkinson's disease. He had written highly influential research papers as well as review papers on the topic of protein aggregation in Lewy body diseases.