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Gaucher-related synucleinopathies: The examination of sporadic neurodegeneration from a rare (*disease*) angle

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ABSTRACT

Gaucher disease, the most common lysosomal storage disease, is caused by a recessively inherited deficiency in glucocerebrosidase and subsequent accumulation of toxic lipid substrates. Heterozygous mutations in the lysosomal glucocerebrosidase gene (*GBA1*) have recently been recognized as the highest genetic risk factor for the development of α-synuclein aggregation disorders ("synucleinopathies"), including Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Despite the wealth of experimental, clinical and genetic evidence that supports the association between mutant genotypes and synucleinopathy risk, the precise mechanisms by which *GBA1* mutations lead to PD and DLB remain unclear. Decreased glucocerebrosidase activity has been demonstrated to promote α-synuclein misprocessing. Furthermore, aberrant α-synuclein species have been reported to downregulate glucocerebrosidase activity, which further contributes to disease progression. In this review, we summarize the recent findings that highlight the complexity of this pathogenetic link and how several pathways that connect glucocerebrosidase insufficiency with α-synuclein misprocessing have emerged as potential therapeutic targets. From a translational perspective, we discuss how various therapeutic approaches to lysosomal dysfunction have been explored for the treatment of *GBA1*-related synucleinopathies, and potentially, for non-*GBA1*-associated neurodegenerative diseases. In summary, the link between *GBA1* and synucleinopathies has become the paradigm of how the study of a rare lysosomal disease can transform the understanding of the etiopathology, and hopefully the treatment, of a more prevalent and multifactorial disorder.

Contents

Abbreviations: AAV, adeno-associated virus; CNS, central nervous system; DLB, dementia with Lewy bodies; ERAD, endoplasmic reticulum associated-degradation; ERT, enzyme replacement therapy; FDA, Food and Drug Administration; *GBA1*, lysosomal glucocerebrosidase gene; *GBA2*, cytosolic glucocerebrosidase gene; HDAC, histone deacetylase; iPSC, induced pluripotent stem cells; Lamp-2a, lysosomal-associated membrane protein 2a; LRRK2, leucine-rich repeat kinase 2; PCT, pharmacological chaperone therapy; PD, Parkinson's disease; RIPK3, receptor-interacting serine–threonine kinase 3; *SNCA*, α-synuclein gene; SRT, substrate reduction therapy; TFEB, transcription factor EB; VPS35, vacuolar protein sorting 35.

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1. Gaucher disease: a rare lysosomal storage disorder

Gaucher disease is the most common lysosomal storage disease and affects approximately 6000 individuals in the U.S. This disease was first described by Phillipe Gaucher in his doctoral thesis in 1882 (Gaucher, 1882). Dr. Gaucher described a patient who presented with splenomegaly as a result of an increased size of the splenic cells. The enlarged cells (now called "Gaucher cells") and an enlarged spleen have become signs of the disease. A succession of scientific breakthroughs occurred over the following century to ultimately achieve a Food and Drug Administration (FDA)-approved therapy for Gaucher disease in 1991 (Grabowski, 2008).

Gaucher disease is caused by biallelic (homozygous or compound heterozygous) mutations in the glucocerebrosidase (*GBA1*, OMIM 606463) gene (Brady et al., 1966). The *GBA1* gene is located in a gene-rich region on chromosome 1q21 spanning 7.6 kb and including 11 exons. A highly homologous pseudogene is located 16 kb downstream and presents challenges for the molecular analysis of *GBA1* (Winfield et al., 1997). Two in-frame ATG translational initiation sites are found in the *GBA1* gene open reading frame and both give rise to active lysosomal protein (Sorge et al., 1987). Glucocerebrosidase (EC 3.2.1.45) is a 497 amino acid protein of approximately 62 kDa that hydrolyses the β-glucosyl linkage of glucosylceramide and other glycolipids in lysosomes. Glucocerebrosidase requires the coordinated action of saposin C and negatively-charged lipids for maximal activity (Grabowski, 2008). Lysosomal trafficking of glucocerebrosidase involves a specific binding partner, lysosomal integral membrane protein-2 (Limp-2) for ER maturation and correct sorting to the lysosomes (Reczek et al., 2007) through a highly regulated mechanism (Jovic et al., 2012). To date, approximately 300 different mutations have been identified in *GBA1*, including point mutations, frameshift mutations, splice-site alterations, and recombinant alleles that encompass segments of a neighboring pseudogene sequence. The glucocerebrosidase deficiency in Gaucher patients promotes widespread accumulation of substrate glycosphingolipids in various organs, including the brain. Although *GBA1* mutations are typically associated with glucocerebrosidase activity reduction, the exact pathogenic mechanism of Gaucher disease remains unknown. Experimental evidence indicates that reduced glucocerebrosidase activity plays a major role in the pathogenic mechanism. Nevertheless, various alternative mechanisms appear to contribute to the disease presentation, including the misprocessing of the enzyme into the lysosome and an increase in endoplasmic reticulum associated-degradation (ERAD) stress. Furthermore, differing clinical presentations in patients and even siblings who share the same genotype suggest a role for disease modifiers (Cox, 2001; Grabowski, 2008).

Gaucher disease displays a wide spectrum of clinical and pathological features in humans; thus, it has been subclassified according to the involvement of the central nervous system (CNS) structures. The excess accumulation of glucosylceramide in macrophages is the main manifestation in the visceral organs of affected individuals. The lipid accumulation can subsequently lead to hepatosplenomegaly, anemia and thrombocytopenia, bone involvement, and, other less frequent unpredictable clinical manifestations (Grabowski, 2008). These visceral manifestations are common to all variants of Gaucher's disease, but categorical differentiation into neuronopathic (type-2 and type-3) and non-neuronopathic (type-1) variants serves useful clinical purposes. Because of the primary visceral macrophage involvement in type-1 Gaucher disease and the intrinsic difficulties traversing the blood–brain barrier to access the CNS, this variant was the initial focus for the development of enzyme replacement therapies. Although, class 1 Gaucher disease was historically classified by the lack of neurological manifestations, a significant number of patients with type-1 Gaucher disease experience parkinsonism contesting the current classification of Gaucher disease, and suggesting that the three forms of Gaucher disease each involve a different profile of neurological manifestations (Beavan and Schapira, 2013; Grabowski, 2008; Neudorfer et al., 1996; Sidransky and Lopez, 2012).

Two types of therapies are approved for the treatment of the visceral manifestations of Gaucher disease. Enzyme replacement therapy, through the systemic administration of glycan-modified recombinant glucocerebrosidase, can effectively treat the visceral and hematological manifestations of Gaucher disease (variant 1) (Barton et al., 1991). However, this form of enzyme replacement therapy has no effect on CNS pathology in variants 2 and 3 because the recombinant enzyme is unable to traverse the blood brain barrier. An alternative therapeutic approach for Gaucher disease that is less widely used is substrate reduction therapy. This approach inhibits glucosylceramide synthase, thereby reducing the synthesis of its substrate, glucosylceramide, to balance production with the impaired rate of degradation (Cox et al., 2000). To date, treatment with the approved therapies for Gaucher disease (i.e., Imiglucerase, Velaglucerase or Miglustat) has not demonstrated effects on the progression of parkinsonism in patients who present with Gaucher and Parkinson's disease (PD) (Bembi et al., 2003; Kraoua et al., 2011; Rosenbloom et al., 2011).

Twenty years ago, the first successful enzyme replacement therapy was developed for treating Gaucher disease, a monogenic mechanistically "simple" disorder. The recent and unanticipated discovery of a genetic link between Gaucher disease and PD has opened new avenues to study this devastating neurodegenerative disease. The basic and clinical expertise accumulated for the rare disease is helping shed light on the development of therapeutics for more common and complex sporadic forms of disease. The focus of this review is to provide an update on the current understanding of the clinical and mechanistic aspects of this genetic interaction and the various therapeutic approaches under consideration.

2. Parkinson's disease (PD): a common neurodegenerative disorder

PD is the second most common neurodegenerative disorder after Alzheimer's disease affecting more than 7 M patients worldwide. The incidence of PD rises sharply after the fifth decade. PD affects approximately 1–2% of individuals over the age of 65 and its prevalence increases to approximately 4% in those above 85 years. As these demographic age groups are growing rapidly due to general aging of the population and increasing lifespans, neurodegenerative diseases will represent an ever-growing social and economic burden (Schlossmacher, 2007).

Initially described by James Parkinson in 1817 (Parkinson, 1817), sporadic PD patients present with the cardinal motor symptom of bradykinesia and one or several of the following symptoms: resting tremor, rigidity, and postural instability (Schlossmacher, 2007). Despite intense research, the causes of PD are poorly understood, and therapy remains primarily focused on symptoms with no intervention in the disease-causing processes (Goedert et al., 2013). Apart from the motor impairment, PD is associated with a large variety of non-motor symptoms, which substantially erode the quality of life, reduce life expectancy and often respond minimally or not at all to the current therapies (Berg et al., 2013; Chaudhuri and Schapira, 2009).

The scientific view on PD etiology has dramatically changed over the last two decades. Numerous etiologies can lead to parkinsonism and only rare cases can be explained by a single genetic or environmental cause (Klein and Schlossmacher, 2007). Initially thought to be an exclusively sporadic disorder, the association between mutations in the α-synuclein gene (*SNCA*) and familial forms of PD was initially received with skepticism (Polymeropoulos et al., 1997). Since then, multiple studies have confirmed that missense and gene dosage *SNCA* mutations can cause autosomal dominant familial PD (Farrer, 2006). In addition, multiple independent studies have identified and validated a number of genes associated with increased risk for PD (Lill et al., 2012; Nalls et al., 2014). These studies point at some common pathways that might be disrupted in affected neurons, such as protein trafficking and maturation, mitochondrial turnover or endosome-lysosomal function (Bonifati, 2014; Corti et al., 2011; Farrer, 2006). Apart from these rare forms, a combination of genetic and environmental factors are thought to contribute in the majority of parkinsonism cases. PD is considered a complex disease, with a multifactorial etiology that involves the complicated and mostly elusive interaction between an aging brain and several susceptibility genes and environmental risk factors (Klein and Schlossmacher, 2007).

The pathological hallmark of PD is the progressive degeneration of dopaminergic neurons in the *substantia nigra*; this degeneration is accompanied by the accumulation of eosinophilic intracytoplasmic protein inclusions referred to as Lewy bodies and Lewy neurites, which primarily consist of α-synuclein (Spillantini et al., 1997). α-Synuclein pathology distribution correlates with the clinical progression of synucleinopathies (Braak and Braak, 2000). α-Synuclein is a 140 amino acid protein that is highly expressed in neurons, particularly in pre-synaptic terminals where it exists in an equilibrium between a soluble and a membrane-bound state (Burre et al., 2014). The precise function of α-synuclein is not completely understood. Experimental evidence indicates that it plays a key role in the regulation of synaptic vesicle clustering and neurotransmitter release (Bendor et al., 2013; Burre et al., 2014).

The general consensus in the field is that aggregation is the main pathogenic feature of α-synuclein. The close association between α-synuclein aggregation and neurodegenerative phenotypes in human patients and animal models and the fact that accelerated aggregation is a common outcome of most α-synuclein mutations underlines the relevance of abnormal aggregation of this protein in the pathogenesis of the synucleinopathies (Stefanis, 2012; Vekrellis et al., 2011). In addition, toxicity is prevented in variants lacking the ability to form aggregates and agents that prevent the formation of aggregated species confer protection to cellular models overexpressing α-synuclein (Lashuel et al., 2013; Stefanis, 2012). There is less agreement as to which particular species are pathogenic (Lashuel et al., 2013). It has recently been proposed that α-synuclein might occur physiologically as helically folded tetramers that resist aggregation (Bartels et al., 2011; Wang et al., 2011). Under pathological conditions, α-synuclein homeostasis can be disturbed, leading to the formation of aggregates via various forms of potentially toxic oligomeric intermediates (Bartels et al., 2011). α-Synuclein accumulation has been proposed to exert toxic effects through a variety of mechanisms, including a blockade of chaperone-mediated autophagy, an impairment of proteasomal degradation and an increase in endoplasmic reticulum stress (Goedert et al., 2013). Recent work has also provided evidence that misfolded fibrillar forms of α-synuclein self-propagate and spread between interconnected CNS regions. Host-to-graft propagation of α-synuclein-positive Lewy-like pathology was observed in long-term mesencephalic transplants in PD (Kordower et al., 2008; Li et al., 2008). These results provided a working hypothesis to account for the highly predictable pattern of aggregated α-synuclein spreading from the lower brainstem and olfactory bulb into the limbic system and, eventually, to the neocortex (Braak and Braak, 2000) and suggested that a mechanism involving cell-to-cell transmission of pathological proteins contributes to disease progression, similar to the one observed in prion diseases (Desplats et al., 2009; Hansen et al., 2011; Luk et al., 2012, 2009).

3. Gaucher mutations: a common genetic risk for synucleinopathies

The most common genetic risk factor for PD was discovered from an unexpected finding in genetics clinics during studies of patients with Gaucher disease. Initial clinical studies suggested the increased occurrence of parkinsonism in Gaucher disease patients and their obligate carrier family members (Goker-Alpan et al., 2004; Neudorfer et al., 1996). This initial suggestion was validated by a large collaborative group that analyzed selected *GBA1* mutations in more than 5000 PD patients and healthy controls without family history of PD and sequenced the entire coding region in a subset of subjects (Sidransky et al., 2009). These observations have now been substantiated by multiple genetic studies demonstrating an increased frequency of mutations in *GBA1* in patients with PD and dementia with Lewy bodies (DLB) (Beavan and Schapira, 2013). Heterozygote carriers of mutations in the *GBA1* gene have an increased frequency of PD, and approximately 5–10% of sporadic PD patients have *GBA1* mutations, which confirm mutations in this gene as the most important genetic predisposing risk factor for PD identified to date (Beavan and Schapira, 2013; Sidransky et al., 2009).

Initial large genome-wide studies on PD patients failed to identify *GBA1* as a susceptibility gene. These studies sought to determine common variants and therefore missed the increased frequency of numerous rare *GBA1* variants with low penetrance and those that occur on different haplotypes (Rogaeva and Hardy, 2008). The glucocerebrosidase story is now considered a paradigm of "*how an important risk factor for a complex disease can evade detection by systematic analysis; it only came into the radar because of astute clinical observations*" (Rogaeva and Hardy, 2008). Subsequent genome-wide association studies that specifically examined *GBA1* variants confirmed the glucocerebrosidase locus as a risk

factor for PD by focusing on specific single nucleotide polymorphisms in the gene or mapping the identical-by-descent segments (Do et al., 2011; Liu et al., 2011; Nalls et al., 2014; Vacic et al., 2014). The frequency and distribution of *GBA1* mutations vary among populations, hindering comparisons between different patient series. Carrier frequency is quite high among Ashkenazi Jews (about 1 person in 14), and N370S accounts for 70% of the mutant alleles in this population (Beutler and Gelbart, 1993; Horowitz et al., 1993). The carrier frequency in other ethnic groups is less than 1%, with a vast range of *GBA1* mutations reported (Horowitz et al., 1993; Sidransky et al., 2009). Regardless of the populations considered, *GBA1* mutations are 5–7 times more frequent in PD patients than controls (Alcalay et al., 2014; Beavan and Schapira, 2013; Sidransky et al., 2009).

To date, the carrier status of a heterozygous *GBA1* mutation is considered the most common genetic risk factor for an α-synuclein aggregation-associated disorder in the brain (“synucleinopathy”). Abnormal processing and accumulation of α-synuclein, which leads to Lewy body and Lewy neurite formation, are the major characteristics of these incurable diseases (Goedert et al., 2013). Intriguingly, the neuropathological evaluation of brains from select Gaucher disease patients with parkinsonism and PD subjects who carry *GBA1* mutations have revealed classical α-synuclein-positive, ubiquitinated Lewy inclusions (Neumann et al., 2009; Wong et al., 2004). Most inclusions exhibited glucocerebrosidase immunofluorescence in the brains from *GBA1*–mutation carriers (Goker-Alpan et al., 2010), which suggests a pathophysiological link between mutant glucocerebrosidase expression and α-synuclein metabolism. Notably, *GBA1* mutation status has no reported effect on multiple system atrophy (MSA), a progressive neurodegenerative disorder characterized by α-synuclein deposits in oligodendroglial cytoplasmic inclusions (Goker-Alpan et al., 2006; Segarane et al., 2009; Srulijes et al., 2013), which might imply different mechanisms for α-synuclein accumulation in neuronal and glial cells. Evaluation of larger cohorts of MSA patients will be required to confirm the lack of association between *GBA1* mutation status and diseases with oligodendroglial α-synuclein inclusions. Lastly, two studies have now shown increased α-synuclein oligomerization in plasma and red blood cells from patients with *GBA1* mutations (Argyriou et al., 2012; Pchelina et al., 2014). These findings will need to be confirmed in larger studies to understand the predictive value of these α-synuclein species for identification of individuals at risk of developing PD.

Further evidence for the role of glucocerebrosidase in synucleinopathies was revealed in genetic studies that demonstrated *SCARB2* gene polymorphisms are associated with PD and DLB (Bras et al., 2014; Do et al., 2011; Hopfner et al., 2013; Michelakakis et al., 2012). The *SCARB2* gene encodes Limp-2, a protein that is critical for glucocerebrosidase transport to the lysosome (Reczek et al., 2007) and has also been shown to regulate glucocerebrosidase enzymatic activity (Rothaug et al., 2014). Correspondingly, Limp-2 knockout mice have recently been shown to present α-synuclein accumulation in the CNS (Rothaug et al., 2014).

Clinical and genetic studies suggest a gene dosage effect in the association between *GBA1* mutations and the development of synucleinopathies. The odds ratio of harboring severe heterozygote *GBA1* mutations (i.e., IVS 2 + 1, 84GG, D409H) was 13.6 compared to an odds ratio of only 2.2 for the milder *GBA1* mutations such as N370S (Gan-Or et al., 2008). In line with these data, carriers of severe *GBA1* mutations had a substantially decreased age at PD onset, compared to carriers of mild mutations, while patients homozygous or compound heterozygous for *GBA1* mutations had the earliest age at onset (Gan-Or et al., 2008). The *GBA1* gene dosage effect on the onset or age-specific risk for PD has been confirmed by several independent reports (Alcalay et al., 2014; Barrett et al., 2013; Becker et al., 2013; Bultron et al., 2010; Nichols et al., 2009; Sidransky et al., 2009). For example, the age-specific risk for PD among Ashkenazi Jewish individuals at 70 years-old was 0.7% for non-mutation carriers; 3.5% for carriers of the *GBA1* N370S “mild” mutation; 5.2% for obligate *GBA1* carriers and 9.1% for patients with Gaucher disease (i.e. *GBA1* homozygotes or compound heterozygotes) (Alcalay et al., 2014). However, it is important to remark that the vast majority of *GBA1* carriers and individuals with homozygous or compound heterozygous *GBA1* mutations will never develop PD (Alcalay et al., 2014). It is likely that additional genetic modifiers and environmental factors influence the disease risk. As more is known about the pathophysiological mechanisms underlying *GBA1*-associated parkinsonism and as potential neuroprotective drugs become available, early identification of those at highest risk will be critical.

4. Clinical features of Gaucher-related PD

The general clinical phenotype of PD patients with *GBA1* mutations is largely indistinguishable from sporadic PD; however, these patients present increased frequencies and severities of motor and non-motor symptoms that substantially erode their quality of life (Beavan and Schapira, 2013). Genetic variation in *GBA1* has emerged as a significant feature impacting the natural history of PD. Patients who carry *GBA1* mutations present a higher prevalence and severity of bradykinesia, motor complications, hyposmia, autonomic impairment, sexual dysfunction, hallucinations, cognitive decline, depression and anxiety (Alcalay et al., 2012; Beavan and Schapira, 2013; Brockmann et al., 2011; Lesage et al., 2010; Li et al., 2014; McNeill et al., 2012; Wang et al., 2014; Winder-Rhodes et al., 2013; Zokaei et al., 2014). Because of the increased rate of clinical decline, patients with *GBA1* mutations often initiate therapies earlier compared with non-mutation carriers (Angeli et al., 2013; Barrett et al., 2014).

Cognitive impairment is one of the most disabling non-motor complications of PD (Alcalay et al., 2012). Post-mortem evaluation of brains from Gaucher patients with parkinsonism and PD subjects who carried *GBA1* mutations have revealed a widespread diffuse hippocampal and neocortical distribution of Lewy bodies, which suggests Lewy body neuropathology may be more extensive in *GBA1* carriers and may be associated with cognitive impairment (Clark et al., 2009; Hall et al., 2014; Neumann et al., 2009; Wong et al., 2004). These findings are in agreement with a study demonstrating that subjects with PD and *GBA1* mutations present reduced resting regional cerebral blood flow in a pattern characteristic of diffuse Lewy body disease (Goker-Alpan et al., 2012). Correspondingly, a mouse model of Gaucher disease has been demonstrated to exhibit memory deficits, as well as progressive accumulation of ubiquitinated α-synuclein aggregates in hippocampal and cortical neurons (Sardi et al., 2011).

Increased cognitive decline has reportedly been the most notable difference observed between PD patients who carry mutant compared with normal *GBA1* alleles. In a recent longitudinal study in unselected cases with PD, heterozygote *GBA1* mutation carriers showed a significantly greater risk for progression to dementia (Winder-Rhodes et al., 2013). Multiple independent studies have confirmed that individuals who carry mutations in *GBA1* have a higher incidence of cognitive impairment and dementia (Agosta et al., 2013; Chahine et al., 2013; Clark et al., 2009; Neumann et al., 2009; Seto-Salvia et al., 2012). In addition, the risk of developing DLB is reportedly three-fold higher than PD, underlying the relevance of *GBA1* mutations on the cognitive function (Asselta et al., 2014; Nalls et al., 2013). Indeed, mutations in *GBA1* are now recognized as an independent risk factor for the development of cognitive impairment in PD patients (Alcalay et al., 2012).

A small pilot study in sporadic PD patients found that increased levels of plasma ceramide and glucosylceramide were associated with cognitive impairment, further implicating the glucocerebrosidase pathway in the development of dementia (Mielke et al., 2013). These findings will need to be confirmed by large longitudinal studies including normal controls and *GBA1* mutation status to understand the predictive value of these lipids and their ability to identify individuals at risk of progressive cognitive impairment.

5. Role of glucocerebrosidase in the development of synucleinopathies

5.1. Reduced glucocerebrosidase increases α-synuclein levels

The role of *GBA1* mutations in the pathogenesis of synucleinopathies is not fully understood, but experimental data indicate that there is a direct relationship between glucocerebrosidase activity and α-synuclein (Fig. 1). Both mutant *GBA1*-mediated loss-of-function and toxic gain-of-function hypotheses have been proposed. Importantly, these two hypotheses are not mutually exclusive, and each scenario is supported by clinical, genetic and experimental evidence (Cullen et al., 2011; Sardi et al., 2011, 2012; Velayati et al., 2010). It is conceivable that in aged humans, *GBA1* heterozygosity promotes α-synuclein misprocessing through two mechanisms, namely, a gain of function effect, which is mediated by its encoded mutant glycoprotein and can be further exacerbated by reduced glucocerebrosidase enzyme activity through a loss of function effect. Thus, both mechanisms may modulate PD susceptibility and lower the observed age of disease onset (Clark et al., 2007; Nichols et al., 2009).

The significance of the glucocerebrosidase activity is underscored by the fact that *GBA1*-null (e.g., 84GG or IVS2 + 1G > A) mutations in humans are associated with a higher risk of the development of synucleinopathies (Gan-Or et al., 2008; Sidransky et al., 2009). In support of the loss of function hypothesis, glucocerebrosidase activity reduction via pharmacological inhibitors or mRNA knock-down strategies can affect α-synuclein homeostasis in cultured cells (Manning-Bog et al., 2009; Mazzulli et al., 2011). In contrast, the effects of *GBA1* mutations independent of activity reduction are more difficult to assess because the presence of mutations generally affects the enzymatic activity. One study reported that the coexpression of wild-type and mutant glucocerebrosidase in mesencephalic cells increased α-synuclein levels with no notable effects on total glucocerebrosidase activity (Cullen et al., 2011). Similarly, the half-life of human α-synuclein in cortical neurons from mice expressing one mutant L444P *Gba1* and one WT allele was increased by more than 70% compared to

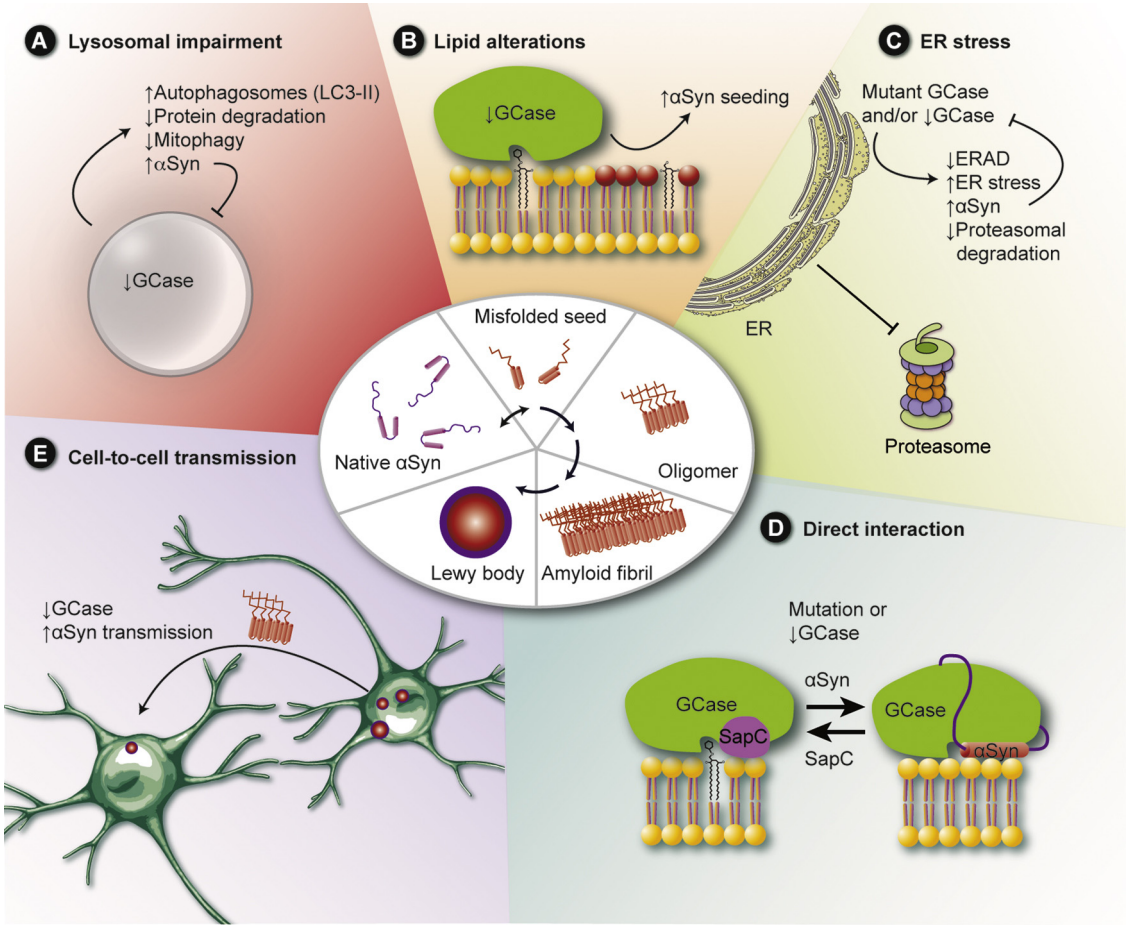

Fig. 1. Potential roles of glucocerebrosidase in the development of synucleinopathies. (A) Decreased glucocerebrosidase activity (GCase) could lead to reduced autophagosomal function, which would result in increased levels of α-synuclein and decreased protein and mitochondrial degradation. (B) Reduction in GCase may alter lipid membrane composition and trigger α-synuclein seeding. (C) Decreased GCase and/or the presence of *GBA1* mutations can overwhelm the ER-associated degradation pathway and lead to α-synuclein accumulation and activation of ER stress signals. (D) Direct binding of α-synuclein to GCase could displace the activator protein saposin C to further decrease the hydrolase activity. (E) Decreased GCase may increase the disease progression via the promotion of cell-to-cell transmission of oligomeric α-synuclein. *Inset*: Hypothetical model for α-synuclein aggregation. Native α-synuclein can undergo misfolding under pathological conditions and oligomerize. Toxic oligomeric α-synuclein continues to form larger amyloid fibrils and subsequent Lewy bodies. See text for details and references.

cells from WT homozygous littermates (Fishbein et al., 2014). In addition, α-synuclein aggregation has been observed in *Gba1* heterozygous mice that carry a mutant (D409V) allele (Sardi et al., 2011).

The effects of glucocerebrosidase activity on α-synuclein accumulation appear to be cell specific because α-synuclein accumulation could not be observed in neuroblastoma cells or primary rat cortical neurons treated with conduritol-B-epoxide (Dermentzaki et al., 2013). Similarly, the overexpression of wild-type glucocerebrosidase in HEK293 cells that expressed A53T α-synuclein and PC12 cells that expressed wild-type α-synuclein induced down-regulation of α-synuclein levels (Cullen et al., 2011). However, this effect was not observed when wild-type glucocerebrosidase was transiently transfected in MES23.5 cells that expressed wild-type α-synuclein (Cullen et al., 2011).

Additional evidence for the role of glucocerebrosidase in α-synuclein homeostasis derives from animal studies. Several independent groups have now reported the presence of α-synuclein accumulation in the brains of mouse models of Gaucher disease carrying different mutations (Cullen et al., 2011; Fishbein et al., 2014; Ginns et al., 2014; Sardi et al., 2011; Xu et al., 2010, 2014). The initial insult caused by the lipid and α-synuclein accumulation can then progress to develop secondary neuroinflammatory pathology, mitochondrial dysfunction or a more profound proteinopathy (Ginns et al., 2014; Sardi et al., 2013; Xu et al., 2014).

Finally, studies have shown that increasing glucocerebrosidase levels can modulate α-synuclein accumulation. Overexpression of wild-type glucocerebrosidase in the hippocampus of a mouse model of Gaucher and synucleinopathy reduced the accumulation of α-synuclein (Sardi et al., 2011, 2013). Correspondingly, dopaminergic neurons from induced pluripotent stem cells (iPSC) generated from patient derived fibroblasts carrying heterozygous *GBA1* mutations (i.e., RecNcil/WT, L444P/WT and N370S/WT) exhibited increased α-synuclein levels that were normalized in their isogenic gene-corrected controls (Schondorf et al., 2014). Recently, iPSC-derived dopamine neurons were generated from monozygotic twins carrying heterozygous *GBA1* N370S mutations and discordant for PD (Woodard et al., 2014). Cells originating from both twins showed increased α-synuclein levels that were reduced by glucocerebrosidase overexpression using a lentiviral vector. Interestingly, α-synuclein cellular distribution differed between the twins with more α-synuclein in the neurites of the affected twin (Woodard et al., 2014). Although the complete mechanistic picture remains unknown, evidence suggests that glucocerebrosidase haploinsufficiency as a result of *GBA1* mutations can interfere with α-synuclein processing and contribute to the pathological accumulation of the protein.

5.2. Glucocerebrosidase deficits and lysosomal dysfunction

Maintaining the fine balance between the synthesis and degradation of molecules and organelles is critical for cellular homeostasis and proper cellular function. Neurons are particularly vulnerable to alterations in the autophagy machinery as evidenced by the brain sensitivity to mutations in genes involved in the global lysosomal network (autophagy and endosomal pathway) and in primary lysosomal disorders (Nixon, 2013). The autolysosomal pathway plays a central role in the degradation of bulky material, including misfolded proteins and damaged organelles; mutations in genes involved in this pathway have increasingly been linked to the synucleinopathies. The autolysosomal pathway plays a central role in the degradation of bulky material, including misfolded proteins and damaged organelles; mutations in genes involved in this pathway have increasingly been linked to the synucleinopathies (Dehay et al., 2013; Tofaris, 2012). Mutations in *PINK1* (encoding for PTEN-induced putative kinase 1), *PARK2* (encoding for Parkin, an E3 ubiquitin ligase) and *ATP13A2* (encoding the protein ATP13A2, a lysosomal type 5 P-type ATPase) cause autosomal recessive early-onset parkinsonism. PINK1 and Parkin play a key role in the maintenance of healthy mitochondria by participating in lysosome-dependent degradation of damaged mitochondria through autophagy (Ashrafi and Schwarz, 2013). Mutations in lysosomal membrane protein ATP13A2 cause familial Kufor–Rakeb syndrome characterized by early onset parkinsonism, pyramidal degeneration and dementia. These mutations lead to general lysosomal alterations in patient-derived fibroblasts, including reduced degradation of lysosomal substrates, and diminished lysosomal-mediated clearance of autophagosomes (Dehay et al., 2012; Usenovic et al., 2012). ATP13A2-mediated lysosomal dysfunction can result in accumulation of α-synuclein and toxicity in mouse primary cortical neurons (Usenovic et al., 2012). Mutations in the *VPS35* (vacuolar protein sorting 35) and *LRRK2* (encoding the Leucine-rich repeat kinase 2) genes, associated to autosomal dominant disease, also implicate the autolysosomal pathway in the pathogenesis of PD. Recent work has shown that disease-causing mutation in VPS35 restricts autophagosome formation, impairs lysosomal degradation of α-synuclein and exacerbates neuronal vulnerability to PD-relevant cellular stress (Miura et al., 2014; Tsika et al., 2014; Zavodszky et al., 2014). Studies with LRRK2 mutants implicated in autosomal dominant PD incriminated this kinase in the regulation of both macroautophagy and chaperone-mediated autophagy (Alegre-Abarrategui et al., 2009; Orenstein et al., 2013).

Several independent studies have reported autolysosomal dysfunction caused by glucocerebrosidase insufficiency. The inhibition of glucocerebrosidase activity by pharmacological inhibitors or mRNA silencing strategies has led to decreased lysosomal protein turnover and accumulation of lysosomal-associated membrane protein-1 structures and autophagosomes per LC3-II buildup in various neuronal cell models (Bae et al., 2014; Dermentzaki et al., 2013; Gegg et al., 2012; Mazzulli et al., 2011; Osellame et al., 2013). Autophagy and lysosomal dysfunction have also been reported in models and tissue samples from subjects with *GBA1*-associated PD (Gegg et al., 2012; Schondorf et al., 2014). In addition, a lack of glucocerebrosidase caused an accumulation of dysfunctional mitochondria secondary to impaired autophagy and dysfunctional proteasomal pathways (Cleeter et al., 2013; Osellame et al., 2013).

Normal lysosomal function is critical for the regulation of α-synuclein homeostasis, as this protein is degraded primarily through lysosomal autophagic mechanisms (Cuervo et al., 2004) (Martinez-Vicente and Cuervo, 2007). The primary lysosomal dysfunction and lipid accumulation caused by decreased glucocerebrosidase activity may subsequently stimulate α-synuclein accumulation. Importantly, the buildup of α-synuclein would then propel to further impairment of the lysosomal and proteosomal degradative machineries (Lindersson et al., 2004; Martinez-Vicente et al., 2008), thereby leading to a more generalized dysfunction and increased neuronal vulnerability to stressors (see Fig. 1).

5.3. Glucocerebrosidase decline and lipid alterations

Membrane lipid interactions with α-synuclein have been strongly associated with the biological and pathological functions of α-synuclein. Alterations in membrane lipid composition can contribute to α-synuclein aggregate seeding (Bendor et al., 2013). Glucocerebrosidase deficits in Gaucher disease cause marked glycolipid accumulation. For example, glucosylceramide and glucosylsphingosine accumulation has been observed in the CNS of neuropathic Gaucher disease patients with decreased

glucocerebrosidase activity (Nilsson and Svennerholm, 1982; Orvisky et al., 2002).

Evidence for glucocerebrosidase substrate accumulation in whole-brain lysates from animals or patients who carry heterozygous mutations in *GBA1* has been elusive (Sardi et al., 2011). A recent report demonstrated increased glucosylceramide levels in iPSC-derived dopaminergic-enriched neuronal cultures from *GBA1* mutation carriers with parkinsonism after more than 70 days in vitro (Schondorf et al., 2014). These studies suggest that specific cell types present selective vulnerability to lipid pathway modifications (Farfel-Becker et al., 2014) and highlight the difficulty in determining lipid alterations in defined cell populations in brain tissue, where small changes might be concealed by the contribution of different cell types. In addition, the subcellular localization of lipids has been reportedly affected by decreased glucocerebrosidase activity (Hein et al., 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. Remarkably, α-synuclein is localized to lipid rafts in neuronal cells (Fortin et al., 2004), and glucosylceramide has been described to directly promote α-synuclein oligomerization (Mazzulli et al., 2011). Therefore, it is speculated that lipid changes induced by partial glucocerebrosidase deficiency may alter the interaction between lipid microdomains and α-synuclein, which might, in turn, lead to synaptic dysfunction and selective neuronal demise (Farfel-Becker et al., 2014; Ginns et al., 2014).

A selective reduction in total ceramide but not sphingomyelin has recently been reported in early stage PD anterior cingulate cortex (Murphy et al., 2014). Ceramide reduction was observed in brain regions that accumulate α-synuclein and glucocerebrosidase deficiency. However, these findings are difficult to associate to the decrease in glucocerebrosidase activity as no decrease in ceramide levels are observed in Gaucher disease mouse brains lacking glucocerebrosidase expression (Farfel-Becker et al., 2014) or in patients with Gaucher disease (Almeida, 2012). The ceramide metabolism dysfunction might suggest significant changes in neuronal membrane properties in PD patients (Fabelo et al., 2011).

5.4. Glucocerebrosidase effects on endoplasmic reticulum stress

The accumulation of misfolded proteins in the brain is a salient feature of PD and other neurodegenerative diseases. To maintain balanced cell proteostasis, aberrant proteins are turned over via endoplasmic reticulum-associated degradation (ERAD) through ubiquitination and proteosomal degradation (Mercado et al., 2013). The accumulation of misfolded proteins that cannot be effectively removed by ERAD leads to ER stress and activates the unfolded protein response that can ultimately elicit apoptosis. ER stress is thought to play crucial roles in the cellular pathology of dopaminergic neurons (Mercado et al., 2013).

Under physiological conditions, newly synthesized glucocerebrosidase is correctly folded in the endoplasmic reticulum and glycosylated in the Golgi prior to arrival at the lysosome. In contrast, mutant glucocerebrosidase can be recognized as misfolded in the ER and undergo ERAD, cytoplasmic retrotranslocation and ubiquitination followed by proteasomal degradation (Ron et al., 2010). The persistent presence of mutant, misfolded glucocerebrosidase molecules in the ER can eventually lead to ER stress and evoke the unfolded protein response (Maor et al., 2013). However, acute inhibition of glucocerebrosidase with the pharmacological inhibitor, CBE, reportedly stimulated ER stress in neuroblastoma cells, which indicates enzymatic activity may also play a role independent of the presence of a pathogenic mutation (Korkotian et al., 1999; Kurzawa-Akanbi et al., 2012). In addition, a neuropathic Gaucher disease mouse model that lacks glucocerebrosidase expression in neurons and macroglia displays neuronal dilations of the ER cisternae at early stages of storage, which further suggests a role of glucocerebrosidase activity in ER homeostasis (Farfel-Becker et al., 2014). Therefore, the predisposition to ER stress in cells that carry glucocerebrosidase defects might be a combined effect of the presence of mutant protein and the loss of glucocerebrosidase enzymatic activity.

5.5. Direct interaction between glucocerebrosidase and α-synuclein

Initial immunofluorescence studies on brain tissue samples from patients with parkinsonism associated with glucocerebrosidase mutations demonstrated that glucocerebrosidase was present in most Lewy bodies, which indicates glucocerebrosidase can be an important component of α-synuclein-positive pathological inclusions (Goker-Alpan et al., 2010). Subsequent biochemical studies have reported a direct physical interaction between glucocerebrosidase and α-synuclein under acidic conditions, which mimics the lysosomal lumen (Yap et al., 2011). The same group later demonstrated that the membrane-bound α-helical form of α-synuclein interacted with glucocerebrosidase and inhibited its hydrolase activity (Yap et al., 2013b) and that the sphingolipid activator protein saposin C protected glucocerebrosidase from α-synuclein inhibition by competing for its binding (Yap et al., 2013a). Accordingly, α-synuclein knockout mice reportedly Exhibit 35% increase in glucocerebrosidase activity without affecting the overall level of enzyme (Fishbein et al., 2014), supporting the in vitro observation of the inhibitory effect of membrane-bound α-synuclein.

Saposin C is an essential activator of glucocerebrosidase, and saposin C deficiency causes Gaucher disease (Tamargo et al., 2012). In vivo studies have also revealed saposin C as a modifier of α-synuclein homeostasis. Mouse models of Gaucher disease that carry hypomorphic forms of the saposin C precursor prosaposin present a more aggressive form of Gaucher disease with profound neurological involvement and deficits in CNS autophagy and proteostasis, which lead to the accumulation of misfolded proteins, including α-synuclein (Xu et al., 2014). Taken together, the relief of α-synuclein-mediated inhibition of glucocerebrosidase activity by saposin C and the accumulation of α-synuclein in prosaposin deficient models implicate glucocerebrosidase activity dysfunction as a critical driver of disease pathogenesis in *GBA1*-associated synucleinopathies.

5.6. Glucocerebrosidase affects α-synuclein cell-to-cell transfer

An emerging field of study in PD and other neurodegenerative diseases is the significance of cell-to-cell transfer of misfolded proteins as a mechanism of disease propagation (Goedert et al., 2013). In the case of synucleinopathies, several independent reports have demonstrated that α-synuclein aggregates are transmitted through exocytosis and subsequent endocytosis between neighboring cells (Lee et al., 2010). Studies have shown that α-synuclein might be released by exocytosis in a calcium-dependent manner (Emmanouilidou et al., 2010; Lee et al., 2005). The effects of glucocerebrosidase deficiency on α-synuclein release have not yet been reported. It is conceivable that glucocerebrosidase depletion would increase α-synuclein release, as lysosomal impairment exacerbates this phenomenon (Alvarez-Erviti et al., 2011).

Extracellular α-synuclein has been demonstrated to have neurotoxic properties and the ability to enhance the aggregation process of endogenous α-synuclein through a seeding process, which therefore contributes to the formation of Lewy body-like inclusions (Hansen et al., 2011; Luk et al., 2009). Although the intrinsic mechanisms are still under investigation, studies have demonstrated that endolysosomal dysfunction increases α-synuclein uptake (Alvarez-Erviti et al., 2011; Lee et al., 2014). Consistent

with these results, a recent manuscript has reported increased neuronal cell-to-cell transmission of endogenous α-synuclein upon glucocerebrosidase knock-down using a zinc finger nuclease approach (Bae et al., 2014). The in vivo relevance of the pathogenic α-synuclein transmission was demonstrated by transplanting normal and *GBA1*$^{-/-}$ SH-SY5Y cells into the hippocampus of transgenic mice expressing human α-synuclein. Analysis of host-derived α-synuclein showed increased transmission in grafted cells lacking glucocerebrosidase compared to controls (Bae et al., 2014). Interestingly, and in agreement with previous studies (Sardi et al., 2011), the authors showed that the ectopic expression of wild-type glucocerebrosidase, but not an activity-deficient mutant, reversed the effects of *GBA1* deletion on the propagation of α-synuclein aggregates, indicating that the hydrolase enzymatic activity is required for the spread of α-synuclein (Bae et al., 2014). Collectively, these studies support the notion that the augmentation of glucocerebrosidase activity might provide a disease modifying therapy and suggest that restoration of the protein's activity may retard the propagation of Lewy pathology, thereby halting the progression of PD.

6. A chronic vicious cycle: α-synuclein effects on glucocerebrosidase. Relevance for sporadic forms of PD

The exact molecular mechanisms implicated in the interaction between *GBA1* gene mutations and the increased risk of synucleinopathies remains unresolved. Importantly, the reciprocal relationship between α-synuclein and glucocerebrosidase is increasingly gaining traction. This relationship is particularly relevant to understand the pathogenic role of glucocerebrosidase in sporadic forms of the disease in patients with two wild-type *GBA1* alleles. As previously reviewed, several lines of evidence have demonstrated that a decrease in glucocerebrosidase activity promotes an increase in α-synuclein levels. Conversely, studies have also shown that α-synuclein buildup can promote glucocerebrosidase deficiency. Overexpression of α-synuclein in neuronal cells and mouse brain prompted a specific decrease in glucocerebrosidase activity without affecting other lysosomal enzymes (Gegg et al., 2012; Mazzulli et al., 2011; Parnetti et al., 2014; Sardi et al., 2012, 2013; Schondorf et al., 2014; Yap et al., 2013b). The mechanisms responsible for this inhibitory effect are still under investigation. Experimental evidence has been put forward suggesting that α-synuclein might impair ER to Golgi trafficking of glucocerbrosidase or directly inhibit the enzyme in the lysosomal compartment (Gegg et al., 2012; Mazzulli et al., 2011; Sardi et al., 2012, 2013; Yap et al., 2013b). Consistently, the decline in glucocerebrosidase activity by α-synuclein accumulation was also described in brain tissues of sporadic PD patients despite carrying two wild-type *GBA1* alleles (Gegg et al., 2012; Parnetti et al., 2014; Schondorf et al., 2014). The bidirectional effects of α-synuclein and glucocerebrosidase form a positive feedback loop that, after a threshold, may lead to a self-propagating disease.

The bidirectional link between α-synuclein and glucocerebrosidase activity is also supported by studies in individuals with no known mutations in *GBA1*, which suggests the analysis of CSF glucocerebrosidase activity and the ratio of oligomeric/total α-synuclein could help to discriminate early stages of PD from neurological controls (Parnetti et al., 2014). Accordingly, a recent report has demonstrated that glucocerebrosidase deficits in early sporadic PD brains from patients carrying wild-type *GBA1* are directly associated with abnormal accumulation of α-synuclein and substantial alterations in lysosomal autophagy function before the establishment of neuronal loss (Murphy et al., 2014).

Various pathogenic pathways might conspire to promote α-synuclein-dependent glucocerebrosidase insufficiency (Fig. 1). For example, the accumulation of α-synuclein has been demonstrated to inhibit lysosomal translocation of newly synthesized proteins, including glucocerebrosidase (Chung et al., 2013; Cooper et al., 2006; Mazzulli et al., 2011). Therefore, in sporadic PD cases, if the delicate balance of α-synuclein homeostasis is disturbed by an impairment of essential protein turnover pathways, such as the unfolded protein response, ERAD, autophagy, cell stress or environmental factors, the increase in α-synuclein levels might inhibit translocation of glucocerebrosidase from the ER to the lysosome. The decreased ER trafficking could lead to reduced glucocerebrosidase activity, which has been observed in the brains of mice overexpressing α-synuclein and PD patients who carried normal *GBA1* alleles (Gegg et al., 2012; Sardi et al., 2013). Alternatively, lysosomal glucocerebrosidase activity might be inhibited by direct α-synuclein interaction as previously described (Yap et al., 2011). In turn, less lysosomal glucocerebrosidase could eventually lead to a gradual increase in the glucocerebroside substrate and subsequent oligomerization and accumulation of α-synuclein that completes the vicious cycle (Mazzulli et al., 2011).

Mechanistically, positive feedback loops are extremely difficult to dissect, and the identification of the trigger for the cascading loop is virtually impossible and is not required to halt the chain of events. In the case of *GBA1* mutation carriers, the trigger of the feedback loop would presumably be the reduced hydrolase activity. In sporadic patients, the idiopathic accumulation of α-synuclein might initiate the feedback mechanism, which subsequently leads to a decrease in glucocerebrosidase activity and additional α-synuclein buildup. Regardless of the initial trigger, glucocerebrosidase augmentation in the CNS has been proposed to slow disease progression and even reverse several pathological manifestations of synucleinopathies, independent of the presence of *GBA1* mutations (Bae et al., 2014; Sardi et al., 2011, 2013).

7. Potential Gaucher targets as therapeutic approaches for Gaucher-associated PD

7.1. Glucocerebrosidase augmentation as a therapeutic approach for Gaucher-associated PD

There are many challenges that need to be overcome to develop disease-modifying therapies for PD. The identification of *GBA1* mutations as the most important risk factor for the development of synucleinopathies has provided a credentialed target validated through human genetics and animal experiments (Alcalay et al., 2012, 2014; Bae et al., 2014; Richter et al., 2014; Sardi et al., 2012, 2013; Schondorf et al., 2014; Sidransky et al., 2009). Animal and cell culture experiments support the notion that increasing glucocerebrosidase activity can lower α-synuclein levels and the associated toxicity (Cullen et al., 2011; Sardi et al., 2011). For example, CNS augmentation of glucocerebrosidase in a symptomatic mouse model of Gaucher-related synucleinopathy has been demonstrated to reduce the accumulation of α-synuclein aggregates and correct the memory impairment in pre- and post-symptomatic animals (Sardi et al., 2011, 2013). Consistent with these results, a recent report has demonstrated that increase in the hydrolase activity of glucocerebrosidase is required for the salutary effects as expression of wild-type enzyme, but not a catalytically-inactive mutant (E235K), rescued the effects of *GBA1* deletion on the cell-to-cell transmission of α-synuclein aggregates (Bae et al., 2014). Hence, it has been proposed that increasing glucocerebrosidase activity in the CNS may slow disease progression and "reverse", at least in part, several pathological manifestations associated with Gaucher-related synucleinopathies. Further validation for this approach has recently been suggested by a report describing significant reduction in plasma oligomeric α-synuclein in Gaucher patients receiving glucocerebrosidase

enzyme replacement therapy for more than 5 years compared to patients not undergoing treatment (Pchelina et al., 2014).

Because of its involvement in Gaucher disease, there is considerably more scientific knowledge and clinical experience in *GBA1* compared with other PD-related genes or potential therapeutic strategies.

This section focuses only on putative therapeutics that target the glucocerebrosidase pathway as a disease-modifying approach for Gaucher-related PD and potentially for sporadic PD. Other potential disease modifying treatments, including neurorestoration and neuroprotection, with mechanisms of action that do not directly impact this lysosomal hydrolase pathway are not discussed here.

7.1.1. Direct enzyme augmentation via enzyme replacement therapy (ERT)

Gaucher disease is characterized by a deficiency of glucocerebrosidase activity and subsequent lysosomal accumulation of undegraded substrates. Glycosyl-modified recombinant human glucocerebrosidase is routinely administered to patients with Gaucher disease as enzyme replacement therapy (ERT). This treatment has been demonstrated to stabilize or reverse several features of Gaucher disease that result from hematologic, visceral, and skeletal involvement. Since 1992, enzyme replacement with recombinant glucocerebrosidase has become the standard of care for patients with non-neuronopathic (type 1) Gaucher disease (Grabowski et al., 1998; Pastores, 2010). ERT is also given to a majority of Gaucher disease type 3 patients, as a means of addressing their systemic symptoms. However, this therapy does not address the CNS manifestations of the disease because the recombinant enzyme is unable to traverse the blood–brain barrier (Pastores, 2010). Brain glucocerebrosidase augmentation has been proposed as a therapy to address the neurological manifestations of Gaucher disease types 2 and 3 (Lonser et al., 2007). Preclinical efforts have been directed at enzyme replacement therapies with CNS-targeting motifs (Spencer and Verma, 2007; Watts and Dennis, 2013), as well as direct brain infusions of recombinant enzyme (Cabrera-Salazar et al., 2010; Ziegler et al., 2011). In addition, these approaches must demonstrate that therapeutic levels and widespread brain distribution of the enzyme can be achieved.

7.1.2. Glucocerebrosidase augmentation via gene delivery

During the previous decade, various gene therapy clinical trials for PD have been initiated and completed. Both adeno-associated virus (AAV) and lentivirus vector platforms have been demonstrated to provide a safe, controlled, highly persistent expression of biologically active proteins to target structures in the human brain (Bartus et al., 2014). In addition, preclinical studies have demonstrated that glucocerebrosidase augmentation via AAV1 can reverse cognitive deficits in a mouse model of Gaucher-related synucleinopathy and decrease α-synuclein in the A53T-alpha-synucleinopathy mouse model (Sardi et al., 2013). Importantly, a widespread increase in glucocerebrosidase activity in the CNS may be required for clinical translation of the therapeutic benefit.

The development of gene therapy as a therapeutic strategy for lysosomal storage disorders has also made considerable progress over the past several years (Cheng, 2014). The premise of gene therapy for this group of diseases is borne of findings that genetic modification of a subset of cells can provide a more global benefit by virtue of the ability of the secreted lysosomal enzymes to effect cross correction of adjacent and distal cells (Fratantoni et al., 1968). Although initial indications from these studies are encouraging, it is evident that second-generation vectors that exhibit a greater safety profile and transduction activity may be required before this optimism can be fully realized (Cheng, 2014). Several recent studies have suggested that some AAV serotypes could achieve extensive CNS distribution in non-human primates (Passini et al., 2014; Yang et al., 2014a). However, the optimal serotype, route of delivery and brain distribution to critical brain regions must be further investigated prior to the development of glucocerebrosidase gene therapy for conditions requiring widespread distribution of therapeutic proteins in the CNS, including lysosomal storage diseases and Gaucher-related PD.

7.1.3. Pharmacological chaperone therapy (PCT)

The use of pharmacological chaperones has also been proposed for Gaucher disease as an alternative to ERT. Pharmacological chaperone therapy (PCT) is based on the use of chaperone molecules that can assist in the folding of the mutated enzyme in the endoplasmic reticulum and improves their stability and lysosomal trafficking (Boyd et al., 2013; Trapero and Llebaria, 2013). This approach is mutation specific and is not amenable to certain mutations that involve large insertions or deletions, frameshifts or premature stop codons that lead to no protein expression. In addition, most pharmacological chaperones that have been identified bind to the catalytic site and inhibit the enzymatic activity, which thus requires chaperone dissociation to permit substrate hydrolysis. The first glucocerebrosidase chaperone to undergo clinical trials was isofagomine (i.e., afegostat-tartrate or AT2101). At low concentrations, isofagomine reportedly promotes a rise in glucocerebrosidase activity. Isofagomine binding to nascent enzyme in the ER permits its further maturation through the ER/Golgi network, thereby reducing the degradation rate of misfolded glucocerebrosidase and promoting its successful transfer to the lysosomes (Lieberman et al., 2007). A small trial in Gaucher patients who used isofagomine lacked adequate clinical improvement in key outcome measures, and further clinical development for this indication was discontinued (Boyd et al., 2013).

The interest in this class of therapeutics might be revitalized as preclinical studies have reported that glucocerebrosidase chaperones can affect α-synuclein processing. Isofagomine treatment of PC12 cells overexpressing human α-synuclein and mutant glucocerebrosidase showed a nonsignificant trend in reducing α-synuclein concentrations (Cullen et al., 2011). A more recent report described that oral administration of isofagomine to α-synuclein transgenic mice for 4 months increased the brain glucocerebrosidase activity, improved olfactory deficits in the buried pellet test and partially recovered motor function using two different tests to evaluate balance and coordination (Richter et al., 2014). In addition, histopathological analysis showed that isofagomine treatment reduced the number of activated microglia in the substantia nigra and altered the size of the insoluble α-synuclein aggregates, suggesting that modulation of glucocerebrosidase by the chaperone might affect α-synuclein cellular processing (Richter et al., 2014). In a different study, treatment with the FDA-approved mucolytic ambroxol, which was previously reported to stabilize glucocerebrosidase (Maegawa et al., 2009; Zimran et al., 2013), reduced oxidative stress and α-synuclein levels in an overexpressing neuroblastoma cell line (McNeill et al., 2014).

A novel class of glucocerebrosidase non-inhibitor chaperones has begun to emerge (Patnaik et al., 2012). Screening for compounds that activate mutant glucocerebrosidase yielded a series of pyrazolopyrimidine derivatives that are both biochemical activators and chaperones of glucocerebrosidase. Some of these compounds increased both wild-type and mutant glucocerebrosidase activities, as well as increased the amounts of enzyme localized to the lysosomes in the fibroblasts obtained from Gaucher patients (Patnaik et al., 2012). A medicinal chemistry optimized analog derived from the pyrazolopyrimidine series

(NCGC00188758) has recently been reported to increase glucocerebrosidase activity and reduce glycolipid storage in monocyte-derived and induced pluripotent stem cell-derived macrophages obtained from Gaucher disease patients who carry different mutations (Aflaki et al., 2014). Another series of salicylic acid derivatives has recently been demonstrated to increase glucocerebrosidase activity and promote lysosomal translocation (Rogers et al., 2012).

The non-inhibitor chaperones have a unique advantage over existing chaperones in that they do not block the enzyme active site; in fact, these compounds increase the enzymatic activity of wild-type glucocerebrosidase through mechanisms still not defined. The evaluation of the effects of these compounds in normal and disease models would be essential to define their ability to attain the required CNS levels to achieve a therapeutic effect. This therapeutic intervention should be amenable to PD patients harboring a wild-type *GBA1* allele. In addition, this therapeutic approach may also extend to sporadic PD patients who exhibit decreased glucocerebrosidase activity despite carrying two wild-type *GBA1* alleles (Gegg et al., 2012; Parnetti et al., 2014; Schondorf et al., 2014).

7.1.4. Alternative approaches to increase lysosomal glucocerebrosidase

7.1.4.1. Lysosomal enhancement. Lysosomal defects are clearly associated with lysosomal storage diseases and have also been implicated in several late onset neurodegenerative diseases, including PD (Dehay et al., 2013; Tofaris, 2012). The lysosomal pathway plays an important role in the maintenance of cellular homeostasis via the degradation of bulky cytoplasmic material, including damaged organelles and misfolded and accumulated proteins. Genetic and experimental evidence strongly implicates decreased lysosomal function in PD pathogenesis (Bras et al., 2014; Dehay et al., 2010). Parkinsonism has been genetically linked to mutations in lysosomal genes (glucocerebrosidase, *GBA1*; ATPase type-13A2, *ATP13A2*), and lysosomal degradation has been demonstrated to be crucial for the clearance of aggregated α-synuclein, which represents the pathologic hallmark of PD (Cuervo et al., 2004; Dehay et al., 2013). The identification of autophagosomes and lysosomal markers as components of the Lewy bodies in patients with sporadic PD raises the intriguing possibility that pathogenic α-synuclein may initially seed around impaired lysosomes and/or undegraded autophagosomes and grow in size by the continuous deposition of additional undegraded material as the disease progresses. In order to reestablish the degradative homeostatic balance, several avenues can be envisioned to effectively activate the lysosomal-autophagy pathway in neurons. Lentiviral-mediated CNS expression of Beclin 1, a protein required for the initiation of autophagosome formation, was shown to ameliorate the neurodegenerative pathology in α-synuclein models of PD and LBD by inducing autophagy (Spencer et al., 2009). A different approach involved the expression of the lysosomal-associated membrane protein 2a (Lamp2a; Xilouri et al., 2013). Binding of substrates to Lamp2a is the rate-limiting step for chaperone-mediated autophagy. Lamp2a overexpression in different neuronal cellular systems stimulated autophagy and selectively protected against adenoviral-mediated wild-type α-synuclein neurotoxicity. In addition, Lamp2a augmentation through the nigral injection of recombinant adeno-associated virus vectors ameliorated α-synuclein-mediated dopaminergic cell loss by increasing the survival of neurons located in the substantia nigra as well as the axon terminals projecting into the striatum, and these effects were associated with a reduction in total α-synuclein levels and related aberrant species (Xilouri et al., 2013).

The identification of a lysosomal master regulator, transcription factor EB (TFEB), which regulates lysosomal biogenesis and participates in macromolecule clearance, may provide a key to extensive activation of the lysosomal system (Sardiello et al., 2009; Settembre et al., 2013). Enhancement of TFEB function has been demonstrated to stimulate the autophagy-lysosome pathway and promote protein clearance and neuroprotection in mouse models of protein misfolding and oxidative stress (Dehay et al., 2010; Tsunemi et al., 2012). Notably, TFEB function was reported to be deficient in a rodent PD model and in human PD brains. Excess cellular levels of α-synuclein in nigral dopamine neurons prevented TFEB nuclear translocation and was associated to a progressive decline in markers of lysosome function (Decressac et al., 2013; Dehay et al., 2010; Tsunemi et al., 2012). Overexpression of TFEB via adeno-associated virus vectors reversed the lysosomal dysfunction and provided robust neuroprotection via the clearance of α-synuclein oligomers (Decressac et al., 2013; Dehay et al., 2010; Tsunemi et al., 2012). Upregulation of glucocerebrosidase might contribute to the beneficial effects of TFEB, as this transcription factor has been reported to directly bind to the *GBA1* promoter and regulate its expression (Sardiello et al., 2009). More recently, ZKSCAN3, a zinc finger family DNA-binding protein, was identified as a master transcriptional repressor of autophagy that counteracts TFEB activity (Chauhan et al., 2013). The identification of small molecules that are capable of potentiating lysosomal metabolism through the activation of TFEB or the inhibition of ZKSCAN3 would represent a particularly attractive strategy for diseases with lysosomal deficits. The enhancement of the lysosomal function would provide relief to the stressed autophagic mechanisms and may deliver a therapeutic benefit.

7.1.4.2. Trafficking enhancement. Mounting evidence suggests that endoplasmic reticulum-Golgi trafficking defects may contribute to PD pathogenesis. Mutations in VPS35 (vacuolar protein sorting 35), a component of the retromer complex that mediates transport between endosomes and the trans-Golgi network, have been implicated in PD (Vilarino-Guell et al., 2011; Zimprich et al., 2011). In addition, there is compelling evidence that α-synuclein buildup in cells interferes with ER-to-Golgi trafficking in yeast and mammalian cells (Chung et al., 2013; Cooper et al., 2006; Gitler et al., 2008; Thayanidhi et al., 2010). ER-to-Golgi vesicle trafficking blockade by α-synuclein impeded the maturation of several proteins implicated in neurodegeneration, including glucocerebrosidase, and may contribute to the reduction in glucocerebrosidase activity observed in the brains of sporadic PD patients and α-synuclein overexpressing mice (Gegg et al., 2012; Mazzulli et al., 2011; Sardi et al., 2013). Correspondingly, mutations in *SCARB2*, which encodes a protein critical for glucocerebrosidase trafficking to the lysosomes, have been associated with synucleinopathies (Bras et al., 2014; Do et al., 2011; Hopfner et al., 2013; Michelakakis et al., 2012), and certain PD-causing mutations in *GBA1* reportedly increase glucocerebrosidase ER retention because of impaired trafficking (Ron and Horowitz, 2005).

Maturation of wild-type glucocerebrosidase through the ER is a highly regulated process that requires Limp-2, specific phosphatidylinositol kinases and distinctive glycosylation (Jovic et al., 2012; Reczek et al., 2007). Glucocerebrosidase ER retention by α-synuclein or Gaucher-causing mutations has reportedly been alleviated by several alternative approaches. For example, affecting ER calcium homeostasis enhanced the capacity of the molecular chaperone system to fold mutant misfolded glucocerebrosidase and increase its lysosomal targeting (Ong et al., 2010; Wang and Segatori, 2013). Reduction of the levels of ERdj3, an ER resident Hsp40 cochaperone required to deliver client proteins to the heat shock protein 70 (Hsp70/BiP), increased mutant glucocerebrosidase folding and

lysosomal targeting (Tan et al., 2014). Histone deacetylase (HDAC) inhibitors and celastrol increased mutant glucocerebrosidase maturation and lysosomal activity (Lu et al., 2011; Yang et al., 2013, 2014b). Perturbation of the E3 ubiquitin ligase Rsp5/Nedd4 with N-arylbenzimidazole relieved α-synuclein-mediated glucocerebrosidase ER retention in rat primary cortical neurons and iPSC-derived neurons from a PD patient carrying the α-synuclein A53T mutation (Chung et al., 2013).

These approaches provide alternative paths to increase glucocerebrosidase activity and may therefore be beneficial in the reduction of α-synuclein toxicity and the amelioration of PD neuropathology in patients with and without Gaucher mutations. Future research should focus on determining the relative contributions of these pathways in disease pathogenesis.

7.2. Substrate reduction therapy (SRT)

The only other approved therapy for Gaucher disease is an oral, small-molecule approach referred to as substrate reduction therapy (SRT) (Grabowski, 2008). Whereas ERT supplies the missing deficient enzyme, SRT targets the inhibition of a key enzyme in the biosynthesis of glucosylceramide, the major substrate of glucocerebrosidase, which therefore decreases the buildup of toxic glycosphingolipids. N-n-butyl-1-deoxynojirimycin (NB-DNJ, Miglustat) was the first approved SRT; however, as a result of a number of undesired side effects, it may only be used in the treatment of type I Gaucher patients for whom enzyme replacement therapy is unsuitable (Grabowski, 2008). As expected, this compound reduced several glycosphingolipid species, but unexpectedly increased the levels of glucosylceramide in the brain, an effect attributed to the inhibition of the non-lysosomal glucocerebrosidase (*GBA2*) (Ashe *et al.*; Nietupski et al., 2012). Despite this paradoxical effect on the total lipid levels, glucosylceramide synthase inhibitors have been demonstrated to reduce α-synuclein aggregates in the brain of a mouse model of Sandhoff Disease (Ashe et al., 2011) and α-synuclein levels in the primary neurons from A53T-α-synuclein transgenic mice through the stimulation of autophagy flux (Shen et al., 2014).

Novel glucosylceramide synthase inhibitors with better safety profiles are under development. A second-generation glucosylceramide synthase inhibitor, Eliglustat, has demonstrated acceptable safety and efficacy in Gaucher patients treated for 4 years (Lukina et al., 2014). Eliglustat was recently approved by the U.S. Food and Drug Administration for the long-term treatment of adult patients with the Type 1 form of Gaucher disease (Poole, 2014). This second-generation inhibitor selectively blocks glucosylceramide synthase and has no effect on other glycosidases, including lysosomal or cytosolic glucocerebrosidases. As expected, Eliglustat lowers glycosphingolipid levels in animals and humans; however, this compound is a substrate for the P-glycoprotein transporter (MDR1), which results in poor brain distribution. Novel, specific and potent third-generation inhibitors of glucosylceramide synthase with good brain penetration profiles have demonstrated a reduction in glycolipid substrates and a prolongation of the life span in a neuropathic Gaucher disease mouse model (Cabrera-Salazar et al., 2012). The in vivo effect of these glucosylceramide synthase inhibitors on neuronal α-synuclein processing remains to be established.

7.3. Necroptosis regulation

Non-traditional cell death mechanisms have emerged as essential players in chronic neurodegenerative diseases (Lee et al., 2013; Re et al., 2014; Vitner et al., 2014). The modulation of necroptosis, a non-apoptotic form of programmed necrosis, has recently been described to promote survival in a genetic and pharmacological mouse model of neuropathic Gaucher disease (Vitner et al., 2014). The necroptosis pathway has numerous effectors amenable to pharmacological targeting, which include death receptors and various kinases (Vandenabeele et al., 2010). Importantly, the absence of the receptor-interacting serine–threonine kinase 3 (RIPK3) was sufficient to display the salutary effects on the neuropathic Gaucher animals (Vitner et al., 2014), which suggests the therapeutic potential of RIPK3 inhibitors for Gaucher disease. Additional research will be required to fully understand the relevance of this pathway for Gaucher-related PD and the potential use of RIPK3 or other necroptosis inhibitors as a therapeutic approach for *GBA1*-associated PD and related synucleinopathies.

8. Concluding remarks

The association between Gaucher disease and PD has received substantial attention in recent years. Because of the wealth of basic and clinical experience with Gaucher disease, the confirmation of the relationship between glucocerebrosidase gene mutations and PD was received with great expectation. Since then, genetic and experimental studies have validated glucocerebrosidase augmentation in the CNS as a potential therapeutic target for synucleinopathies. In addition, recent insights into the link between glucocerebrosidase and α-synuclein have shed light into the pathogenic mechanisms and suggest that this therapeutic intervention might be beneficial not only for individuals who carry *GBA1* mutations but also for patients who express *GBA1* wild-type alleles. Despite these promising advances, several mechanistic, clinical and epidemiological issues must be further explored to better understand the potential of the different therapeutic interventions.

Mutations in *GBA1* are the most common genetic risk factor for the development of PD or DLB; however, the fact that only a small subgroup of carriers ever develops the disease suggests the presence of genetic and environmental modifiers. It is conceivable that there are unidentified targets capable of rescuing the homeostatic balance between glucocerebrosidase activity and α-synuclein from the pathogenic feedback loop. From the clinical perspective, large prospective longitudinal studies are warranted to understand the natural history and to carefully define the progression of motor and non-motor features of the disease to help guide the initial trials in PD cohorts with and without *GBA1* mutations. Similarly to other neurodegenerative diseases, early detection of patients prior to marked irreversible neuronal loss, as well as appropriate biomarkers to follow disease progression and interventions will prove critical for the advancement of a successful therapeutic strategy.

The success of developing a therapeutic strategy based on this unanticipated link between Gaucher disease and PD will stimulate the reevaluation of other rare diseases in the context of more common forms of disease. Twenty years ago, the first successful enzyme replacement therapy was developed for treating Gaucher disease. Today, the knowledge amassed for Gaucher disease has a new purpose; our experiences with this rare disorder are helping shed light on the development of therapeutics for more common and complex sporadic forms of disease.

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References

Aflaki, E., Stubblefield, B.K., Maniwang, E., Lopez, G., Moaven, N., Goldin, E., Marugan, J., Patnaik, S., Dutra, A., Southall, N., Zheng, W., Tayebi, N., Sidransky, E., 2014. Macrophage models of Gaucher disease for evaluating disease pathogenesis and candidate drugs. Sci. Transl. Med. 6, 240–273.

Agosta, F., Kostic, V.S., Davidovic, K., Kresojevic, N., Sarro, L., Svetel, M., Stankovic, I., Comi, G., Klein, C., Filippi, M., 2013. White matter abnormalities in Parkinson's disease patients with glucocerebrosidase gene mutations. Mov. Disord. 28, 772–778.

Alcalay, R.N., Caccappolo, E., Mejia-Santana, H., Tang, M., Rosado, L., Orbe Reilly, M., Ruiz, D., Ross, B., Verbitsky, M., Kisselev, S., Louis, E., Comella, C., Colcher, A., Jennings, D., Nance, M., Bressman, S., Scott, W.K., Tanner, C., Mickel, S., Andrews, H., Waters, C., Fahn, S., Cote, L., Frucht, S., Ford, B., Rezak, M., Novak, K., Friedman, J.H., Pfeiffer, R., Marsh, L., Hiner, B., Siderowf, A., Payami, H., Molho, E., Factor, S., Ottman, R., Clark, L.N., Marder, K., 2012. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology 78, 1434–1440.

Alcalay, R.N., Dinur, T., Quinn, T., Sakanaka, K., Levy, O., Waters, C., Fahn, S., Dorovski, T., Chung, W.K., Pauciulo, M., Nichols, W., Rana, H.Q., Balwani, M., Bier, L., Elstein, D., Zimran, A., 2014. Comparison of Parkinson risk in Ashkenazi Jewish patients with Gaucher disease and GBA heterozygotes. JAMA Neurol. 71, 752–757.

Alegre-Abarrategui, J., Christian, H., Lufino, M.M., Mutihac, R., Venda, L.L., Ansorge, O., Wade-Martins, R., 2009. LRRK2 regulates autophagic activity and localizes to specific membrane microdomains in a novel human genomic reporter cellular model. Hum. Mol. Genet. 18, 4022–4034.

Almeida, M.R., 2012. Glucocerebrosidase involvement in Parkinson disease and other synucleinopathies. Front. Neurol. 3, 65.

Alvarez-Erviti, L., Seow, Y., Schapira, A.H., Gardiner, C., Sargent, I.L., Wood, M.J., Cooper, J.M., 2011. Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission. Neurobiol. Dis. 42, 360–367.

Angeli, A., Mencacci, N.E., Duran, R., Aviles-Olmos, I., Kefalopoulou, Z., Candelario, J., Rusbridge, S., Foley, J., Pradhan, P., Jahanshahi, M., Zrinzo, L., Hariz, M., Wood, N.W., Hardy, J., Limousin, P., Foltynie, T., 2013. Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. Mov. Disord. 28, 1370–1375.

Argyriou, A., Dermentzaki, G., Papasilekas, T., Moraitou, M., Stamboulis, E., Vekrellis, K., Michelakakis, H., Stefanis, L., 2012. Increased dimerization of alpha-synuclein in erythrocytes in Gaucher disease and aging. Neurosci. Lett. 528, 205–209.

Ashe, K.M., Bangari, D., Li, L., Cabrera-Salazar, M.A., Bercury, S.D., Nietupski, J.B., Cooper, C.G., Aerts, J.M., Lee, E.R., Copeland, D.P., Cheng, S.H., Scheule, R.K., Marshall, J., 2011. Iminosugar-based inhibitors of glucosylceramide synthase increase brain glycosphingolipids and survival in a mouse model of Sandhoff disease. PLoS ONE 6, e21758.

Ashrafi, G., Schwarz, T.L., 2013. The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ. 20, 31–42.

Asselta, R., Rimoldi, V., Siri, C., Cilia, R., Guella, I., Tesei, S., Solda, G., Pezzoli, G., Duga, S., Goldwurm, S., 2014. Glucocerebrosidase mutations in primary parkinsonism. Parkinsonism Relat. Disord. 20, 1215–1220.

Bae, E.J., Yang, N.Y., Song, M., Lee, C.S., Lee, J.S., Jung, B.C., Lee, H.J., Kim, S., Masliah, E., Sardi, S.P., Lee, S.J., 2014. Glucocerebrosidase depletion enhances cell-to-cell transmission of alpha-synuclein. Nat. Commun. 5, 4755.

Barrett, M.J., Giraldo, P., Capablo, J.L., Alfonso, P., Irun, P., Garcia-Rodriguez, B., Pocovi, M., Pastores, G.M., 2013. Greater risk of parkinsonism associated with non-N370S GBA1 mutations. J. Inherit. Metab. Dis. 36, 575–580.

Barrett, M.J., Shanker, V.L., Severt, W.L., Raymond, D., Gross, S.J., Schreiber-Agus, N., Kornreich, R., Ozelius, L.J., Bressman, S.B., Saunders-Pullman, R., 2014. Cognitive and Antipsychotic Medication Use in Monoallelic GBA-Related Parkinson Disease. *JIMD Reports*.

Bartels, T., Choi, J.G., Selkoe, D.J., 2011. α-Synuclein occurs physiologically as a helically folded tetramer that resists aggregation. Nature 477, 107–110.

Barton, N.W., Brady, R.O., Dambrosia, J.M., Di Bisceglie, A.M., Doppelt, S.H., Hill, S.C., Mankin, H.J., Murray, G.J., Parker, R.I., Argoff, C.E., et al., 1991. Replacement therapy for inherited enzyme deficiency – macrophage-targeted glucocerebrosidase for Gaucher's disease. N. Engl. J. Med. 324, 1464–1470.

Bartus, R.T., Weinberg, M.S., Samulski, R.J., 2014. Parkinson's disease gene therapy: success by design meets failure by efficacy. Mol. Ther. 22, 487–497.

Beavan, M.S., Schapira, A.H., 2013. Glucocerebrosidase mutations and the pathogenesis of Parkinson disease. Ann. Med. 45, 511–521.

Becker, J.G., Pastores, G.M., Di Rocco, A., Ferraris, M., Graber, J.J., Sathe, S., 2013. Parkinson's disease in patients and obligate carriers of Gaucher disease. Parkinsonism Relat. Disord. 19, 129–131.

Bembi, B., Zambito Marsala, S., Sidransky, E., Ciana, G., Carrozzi, M., Zorzon, M., Martini, C., Gioulis, M., Pittis, M.G., Capus, L., 2003. Gaucher's disease with Parkinson's disease: clinical and pathological aspects. Neurology 61, 99–101.

Bendor, J.T., Logan, T.P., Edwards, R.H., 2013. The function of alpha-synuclein. Neuron 79, 1044–1066.

Berg, D., Lang, A.E., Postuma, R.B., Maetzler, W., Deuschl, G., Gasser, T., Siderowf, A., Schapira, A.H., Oertel, W., Obeso, J.A., Olanow, C.W., Poewe, W., Stern, M., 2013. Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. Lancet Neurol. 12, 514–524.

Beutler, E., Gelbart, T., 1993. Gaucher disease mutations in non-Jewish patients. Br. J. Haematol. 85, 401–405.

Bonifati, V., 2014. Genetics of Parkinson's disease – state of the art, 2013. Parkinsonism Relat. Disord. 20 (Suppl. 1), S23–S28.

Boyd, R.E., Lee, G., Rybczynski, P., Benjamin, E.R., Khanna, R., Wustman, B.A., Valenzano, K.J., 2013. Pharmacological chaperones as therapeutics for lysosomal storage diseases. J. Med. Chem. 56, 2705–2725.

Braak, H., Braak, E., 2000. Pathoanatomy of Parkinson's disease. J. Neurol. 247 (Suppl. 2), II3–II10.

Brady, R.O., Kanfer, J.N., Bradley, R.M., Shapiro, D., 1966. Demonstration of a deficiency of glucocerebroside-cleaving enzyme in Gaucher's disease. J. Clin. Invest. 45, 1112–1115.

Bras, J., Guerreiro, R., Darwent, L., Parkkinen, L., Ansorge, O., Escott-Price, V., Hernandez, D.G., Nalls, M.A., Clark, L.N., Honig, L.S., Marder, K., Van Der Flier, W.M., Lemstra, A., Scheltens, P., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Ortega-Cubero, S., Pastor, P., Ferman, T.J., Graff-Radford, N.R., Ross, O.A., Barber, I., Braae, A., Brown, K., Morgan, K., Maetzler, W., Berg, D., Troakes, C., Al-Sarraj, S., Lashley, T., Compta, Y., Revesz, T., Lees, A., Cairns, N., Halliday, G.M., Mann, D., Pickering-Brown, S., Dickson, D.W., Singleton, A., Hardy, J., 2014. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum. Mol. Genet. 23, 6139–6146.

Brockmann, K., Srulijes, K., Hauser, A.K., Schulte, C., Csoti, I., Gasser, T., Berg, D., 2011. GBA-associated PD presents with nonmotor characteristics. Neurology 77, 276–280.

Bultron, G., Kacena, K., Pearson, D., Boxer, M., Yang, R., Sathe, S., Pastores, G., Mistry, P.K., 2010. The risk of Parkinson's disease in type 1 Gaucher disease. J. Inherit. Metab. Dis. 33, 167–173.

Burre, J., Sharma, M., Sudhof, T.C., 2014. alpha-Synuclein assembles into higher-order multimers upon membrane binding to promote SNARE complex formation. Proc. Natl. Acad. Sci. U. S. A. 111, E4274–E4283.

Cabrera-Salazar, M.A., Bercury, S.D., Ziegler, R.J., Marshall, J., Hodges, B.L., Chuang, W.L., Pacheco, J., Li, L., Cheng, S.H., Scheule, R.K., 2010. Intracerebroventricular delivery of glucocerebrosidase reduces substrates and increases lifespan in a mouse model of neuronopathic Gaucher disease. Exp. Neurol. 225, 436–444.

Cabrera-Salazar, M.A., Deriso, M., Bercury, S.D., Li, L., Lydon, J.T., Weber, W., Pande, N., Cromwell, M.A., Copeland, D., Leonard, J., Cheng, S.H., Scheule, R.K., 2012. Systemic delivery of a glucosylceramide synthase inhibitor reduces CNS substrates and increases lifespan in a mouse model of type 2 Gaucher disease. PLoS ONE 7, e43310.

Chahine, L.M., Qiang, J., Ashbridge, E., Minger, J., Yearout, D., Horn, S., Colcher, A., Hurtig, H.I., Lee, V.M., Van Deerlin, V.M., Leverenz, J.B., Siderowf, A.D., Trojanowski, J.Q., Zabetian, C.P., Chen-Plotkin, A., 2013. Clinical and biochemical differences in patients having Parkinson disease with vs without GBA mutations. JAMA Neurol. 70, 852–858.

Chaudhuri, K.R., Schapira, A.H., 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet Neurol. 8, 464–474.

Chauhan, S., Goodwin, J.G., Chauhan, S., Manyam, G., Wang, J., Kamat, A.M., Boyd, D.D., 2013. ZKSCAN3 is a master transcriptional repressor of autophagy. Mol. Cell 50, 16–28.

Cheng, S.H., 2014. Gene therapy for the neurological manifestations in lysosomal storage disorders. J. Lipid Res. 55, 1827–1838.

Chung, C.Y., Khurana, V., Auluck, P.K., Tardiff, D.F., Mazzulli, J.R., Soldner, F., Baru, V., Lou, Y., Freyzon, Y., Cho, S., Mungenast, A.E., Muffat, J., Mitalipova, M., Pluth, M.D., Jui, N.T., Schule, B., Lippard, S.J., Tsai, L.H., Krainc, D., Buchwald, S.L., Jaenisch, R., Lindquist, S., 2013. Identification and rescue of alpha-synuclein toxicity in Parkinson patient-derived neurons. Science 342, 983–987.

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., Vonsattel, J.P., Fahn, S., Mayeux, R., Honig, L.S., Marder, K., 2009. Association of glucocerebrosidase mutations with dementia with Lewy bodies. Arch. Neurol. 66, 578–583.

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., Ford, B., Frucht, S., Ottman, R., Marder, K., 2007. Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. Neurology 69, 1270–1277.

Cleeter, M.W., Chau, K.Y., Gluck, C., Mehta, A., Hughes, D.A., Duchen, M., Wood, N.W., Hardy, J., Mark Cooper, J., Schapira, A.H., 2013. Glucocerebrosidase inhibition causes mitochondrial dysfunction and free radical damage. Neurochem. Int. 62, 1–7.

Cooper, A.A., Gitler, A.D., Cashikar, A., Haynes, C.M., Hill, K.J., Bhullar, B., Liu, K., Xu, K., Strathearn, K.E., Liu, F., Cao, S., Caldwell, K.A., Caldwell, G.A., Marsischky, G., Kolodner, R.D., Labaer, J., Rochet, J.C., Bonini, N.M., Lindquist, S., 2006. Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. Science 313, 324–328.

Corti, O., Lesage, S., Brice, A., 2011. What genetics tells us about the causes and mechanisms of Parkinson's disease. Physiol. Rev. 91, 1161–1218.

Cox, T., Lachmann, R., Hollak, C., Aerts, J., van Weely, S., Hrebicek, M., Platt, F., Butters, T., Dwek, R., Moyses, C., Gow, I., Elstein, D., Zimran, A., 2000. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. Lancet 355, 1481–1485.

Cox, T.M., 2001. Gaucher's disease – an exemplary monogenic disorder. QJM 94, 399–402.

Cuervo, A.M., Stefanis, L., Fredenburg, R., Lansbury, P.T., Sulzer, D., 2004. Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science 305, 1292–1295.

Cullen, V., Sardi, S.P., Ng, J., Xu, Y.H., Sun, Y., Tomlinson, J.J., Kolodziej, P., Kahn, I., Saftig, P., Woulfe, J., Rochet, J.C., Glicksman, M.A., Cheng, S.H., Grabowski, G.A., Shihabuddin, L.S., Schlossmacher, M.G., 2011. Acid beta-glucosidase mutants linked to Gaucher disease, Parkinson disease, and Lewy body dementia alter alpha-synuclein processing. Ann. Neurol. 69, 940–953.

Decressac, M., Mattsson, B., Weikop, P., Lundblad, M., Jakobsson, J., Bjorklund, A., 2013. TFEB-mediated autophagy rescues midbrain dopamine neurons from alpha-synuclein toxicity. Proc. Natl. Acad. Sci. U. S. A. 110, E1817–E1826.
Dehay, B., Bove, J., Rodriguez-Muela, N., Perier, C., Recasens, A., Boya, P., Vila, M., 2010. Pathogenic lysosomal depletion in Parkinson's disease. J. Neurosci. 30, 12535–12544.
Dehay, B., Martinez-Vicente, M., Caldwell, G.A., Caldwell, K.A., Yue, Z., Cookson, M.R., Klein, C., Vila, M., Bezard, E., 2013. Lysosomal impairment in Parkinson's disease. Mov. Disord. 28, 725–732.
Dehay, B., Ramirez, A., Martinez-Vicente, M., Perier, C., Canron, M.H., Doudnikoff, E., Vital, A., Vila, M., Klein, C., Bezard, E., 2012. Loss of P-type ATPase ATP13A2/PARK9 function induces general lysosomal deficiency and leads to Parkinson disease neurodegeneration. Proc. Natl. Acad. Sci. U. S. A. 109, 9611–9616.
Dermentzaki, G., Dimitriou, E., Xilouri, M., Michelakakis, H., Stefanis, L., 2013. Loss of beta-glucocerebrosidase activity does not affect alpha-synuclein levels or lysosomal function in neuronal cells. PLOS ONE 8, e60674.
Desplats, P., Lee, H.J., Bae, E.J., Patrick, C., Rockenstein, E., Crews, L., Spencer, B., Masliah, E., Lee, S.J., 2009. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. Proc. Natl. Acad. Sci. U. S. A. 106, 13010–13015.
Do, C.B., Tung, J.Y., Dorfman, E., Kiefer, A.K., Drabant, E.M., Francke, U., Mountain, J.L., Goldman, S.M., Tanner, C.M., Langston, J.W., Wojcicki, A., Eriksson, N., 2011. Web-based genome-wide association study identifies two novel loci and a substantial genetic component for Parkinson's disease. PLoS Genet. 7, e1002141.
Emmanouilidou, E., Melachroinou, K., Roumeliotis, T., Garbis, S.D., Ntzouni, M., Margaritis, L.H., Stefanis, L., 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.
Fabelo, N., Martin, V., Santpere, G., Marin, R., Torrent, L., Ferrer, I., Diaz, M., 2011. Severe alterations in lipid composition of frontal cortex lipid rafts from Parkinson's disease and incidental Parkinson's disease. Mol. Med. 17, 1107–1118.
Farfel-Becker, T., Vitner, E.B., Kelly, S.L., Bame, J.R., Duan, J., Shinder, V., Merrill Jr., A.H., Dobrenis, K., Futerman, A.H., 2014. Neuronal accumulation of glucosylceramide in a mouse model of neuronopathic Gaucher disease leads to neurodegeneration. Hum. Mol. Genet. 23, 843–854.
Farrer, M.J., 2006. Genetics of Parkinson disease: paradigm shifts and future prospects. Nat. Rev. Genet. 7, 306–318.
Fishbein, I., Kuo, Y.M., Giasson, B.I., Nussbaum, R.L., 2014. Augmentation of phenotype in a transgenic Parkinson mouse heterozygous for a Gaucher mutation. Brain 137, 3235–3247.
Fortin, D.L., Troyer, M.D., Nakamura, K., Kubo, S., Anthony, M.D., Edwards, R.H., 2004. Lipid rafts mediate the synaptic localization of alpha-synuclein. J. Neurosci. 24, 6715–6723.
Fratantoni, J.C., Hall, C.W., Neufeld, E.F., 1968. Hurler and Hunter syndromes: mutual correction of the defect in cultured fibroblasts. Science 162, 570–572.
Gan-Or, Z., Giladi, N., Rozovski, U., Shifrin, C., Rosner, S., Gurevich, T., Bar-Shira, A., Orr-Urtreger, A., 2008. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology 70, 2277–2283.
Gaucher, P.C.E., 1882. De l'épithélioma primitif de la rate, hypertrophie idiopathique de la rate sans leucémie. (MD thesis)Paris.
Gegg, M.E., Burke, D., Heales, S.J., Cooper, J.M., Hardy, J., Wood, N.W., Schapira, A.H., 2012. Glucocerebrosidase deficiency in substantia nigra of Parkinson disease brains. Ann. Neurol. 72, 455–463.
Ginns, E.I., Mak, S.K., Ko, N., Karlgren, J., Akbarian, S., Chou, V.P., Guo, Y., Lim, A., Samuelsson, S., LaMarca, M.L., Vazquez-DeRose, J., Manning-Bog, A.B., 2014. Neuroinflammation and alpha-synuclein accumulation in response to glucocerebrosidase deficiency are accompanied by synaptic dysfunction. Mol. Genet. Metab. 111, 152–162.
Gitler, A.D., Bevis, B.J., Shorter, J., Strathearn, K.E., Hamamichi, S., Su, L.J., Caldwell, K.A., Caldwell, G.A., Rochet, J.C., McCaffery, J.M., Barlowe, C., Lindquist, S., 2008. The Parkinson's disease protein alpha-synuclein disrupts cellular Rab homeostasis. Proc. Natl. Acad. Sci. U. S. A. 105, 145–150.
Goedert, M., Spillantini, M.G., Del Tredici, K., Braak, H., 2013. 100 years of Lewy pathology. Nat. Rev. Neurol. 9, 13–24.
Goker-Alpan, O., Giasson, B.I., Eblan, M.J., Nguyen, J., Hurtig, H.I., Lee, V.M., Trojanowski, J.Q., Sidransky, E., 2006. Glucocerebrosidase mutations are an important risk factor for Lewy body disorders. Neurology 67, 908–910.
Goker-Alpan, O., Masdeu, J.C., Kohn, P.D., Ianni, A., Lopez, G., Groden, C., Chapman, M.C., Cropp, B., Eisenberg, D.P., Maniwang, E.D., Davis, J., Wiggs, E., Sidransky, E., Berman, K.F., 2012. The neurobiology of glucocerebrosidase-associated parkinsonism: a positron emission tomography study of dopamine synthesis and regional cerebral blood flow. Brain 135, 2440–2448.
Goker-Alpan, O., Schiffmann, R., LaMarca, M.E., Nussbaum, R.L., McInerney-Leo, A., Sidransky, E., 2004. Parkinsonism among Gaucher disease carriers. J. Med. Genet. 41, 937–940.
Goker-Alpan, O., Stubblefield, B.K., Giasson, B.I., Sidransky, E., 2010. Glucocerebrosidase is present in alpha-synuclein inclusions in Lewy body disorders. Acta Neuropathol. 120, 641–649.
Grabowski, G.A., 2008. Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet 372, 1263–1271.
Grabowski, G.A., Leslie, N., Wenstrup, R., 1998. Enzyme therapy for Gaucher disease: the first 5 years. Blood Rev. 12, 115–133.
Hall, H., Reyes, S., Landeck, N., Bye, C., Leanza, G., Double, K., Thompson, L., Halliday, G., Kirik, D., 2014. Hippocampal Lewy pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease. Brain 137, 2493–2508.
Hansen, C., Angot, E., Bergstrom, A.L., Steiner, J.A., Pieri, L., Paul, G., Outeiro, T.F., Melki, R., Kallunki, P., Fog, K., Li, J.Y., Brundin, P., 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., Duplock, S., Hopwood, J.J., Fuller, M., 2008. Lipid composition of microdomains is altered in a cell model of Gaucher disease. J. Lipid Res. 49, 1725–1734.
Hopfner, F., Schulte, E.C., Mollenhauer, B., Bereznai, B., Knauf, F., Lichtner, P., Zimprich, A., Haubenberger, D., Pirker, W., Brucke, T., Peters, A., Gieger, C., Kuhlenbaumer, G., Trenkwalder, C., Winkelmann, J., 2013. The role of SCARB2 as susceptibility factor in Parkinson's disease. Mov. Disord. 28, 538–540.
Horowitz, M., Tzuri, G., Eyal, N., Berebi, A., Kolodny, E.H., Brady, R.O., Barton, N.W., Abrahamov, A., Zimran, A., 1993. Prevalence of nine mutations among Jewish and non-Jewish Gaucher disease patients. Am. J. Hum. Genet. 53, 921–930.
Jovic, M., Kean, M.J., Szentpetery, Z., Polevoy, G., Gingras, A.C., Brill, J.A., Balla, T., 2012. Two phosphatidylinositol 4-kinases control lysosomal delivery of the Gaucher disease enzyme, beta-glucocerebrosidase. Mol. Biol. Cell 23, 1533–1545.
Klein, C., Schlossmacher, M.G., 2007. Parkinson disease, 10 years after its genetic revolution: multiple clues to a complex disorder. Neurology 69, 2093–2104.
Kordower, J.H., Chu, Y., Hauser, R.A., Freeman, T.B., Olanow, C.W., 2008. Lewy body-like pathology in long-term embryonic nigral transplants in Parkinson's disease. Nat. Med. 14, 504–506.
Korkotian, E., Schwarz, A., Pelled, D., Schwarzmann, G., Segal, M., Futerman, A.H., 1999. Elevation of intracellular glucosylceramide levels results in an increase in endoplasmic reticulum density and in functional calcium stores in cultured neurons. J. Biol. Chem. 274, 21673–21678.
Kraoua, I., Sedel, F., Caillaud, C., Froissart, R., Stirnemann, J., Chaurand, G., Flodrops, H., Tari, S., Gourfinkel-An, I., Mathieu, S., Belmatoug, N., Billette de Villemeur, T., Mignot, C., 2011. A French experience of type 3 Gaucher disease: phenotypic diversity and neurological outcome of 10 patients. Brain Dev. 33, 131–139.
Kurzawa-Akanbi, M., Hanson, P.S., Blain, P.G., Lett, D.J., McKeith, I.G., Chinnery, P.F., Morris, C.M., 2012. Glucocerebrosidase mutations alter the endoplasmic reticulum and lysosomes in Lewy body disease. J. Neurochem. 123, 298–309.
Lashuel, H.A., Overk, C.R., Oueslati, A., Masliah, E., 2013. The many faces of alpha-synuclein: from structure and toxicity to therapeutic target. Nat. Rev. Neurosci. 14, 38–48.
Lee, H.J., Bae, E.J., Lee, S.J., 2014. Extracellular alpha – synuclein-a novel and crucial factor in Lewy body diseases. Nat. Rev. Neurol. 10, 92–98.
Lee, H.J., Patel, S., Lee, S.J., 2005. Intravesicular localization and exocytosis of alpha-synuclein and its aggregates. J. Neurosci. 25, 6016–6024.
Lee, S.J., Desplats, P., Sigurdson, C., Tsigelny, I., Masliah, E., 2010. Cell-to-cell transmission of non-prion protein aggregates. Nat. Rev. Neurol. 6, 702–706.
Lee, Y., Karuppagounder, S.S., Shin, J.H., Lee, Y.I., Ko, H.S., Swing, D., Jiang, H., Kang, S.U., Lee, B.D., Kang, H.C., Kim, D., Tessarollo, L., Dawson, V.L., Dawson, T.M., 2013. Parthanatos mediates AIMP2-activated age-dependent dopaminergic neuronal loss. Nat. Neurosci. 16, 1392–1400.
Lesage, S., Anheim, M., Condroyer, C., Pollak, P., Durif, F., Dupuits, C., Viallet, F., Lohmann, E., Corvol, J.C., Honore, A., Rivaud, S., Vidailhet, M., Durr, A., Brice, A., 2010. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum. Mol. Genet. 20, 202–210.
Li, J.Y., Englund, E., Holton, J.L., Soulet, D., Hagell, P., Lees, A.J., Lashley, T., Quinn, N.P., Rehncrona, S., Bjorklund, A., Widner, H., Revesz, T., Lindvall, O., Brundin, P., 2008. Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. Nat. Med. 14, 501–503.
Li, Y., Sekine, T., Funayama, M., Li, L., Yoshino, H., Nishioka, K., Tomiyama, H., Hattori, N., 2014. Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. Neurobiol. Aging 35 (935), e933–e938.
Lieberman, R.L., Wustman, B.A., Huertas, P., Powe Jr., A.C., Pine, C.W., Khanna, R., Schlossmacher, M.G., Ringe, D., Petsko, G.A., 2007. Structure of acid beta-glucosidase with pharmacological chaperone provides insight into Gaucher disease. Nat. Chem. Biol. 3, 101–107.
Lill, C.M., Roehr, J.T., McQueen, M.B., Kavvoura, F.K., Bagade, S., Schjeide, B.M., Schjeide, L.M., Meissner, E., Zauft, U., Allen, N.C., Liu, T., Schilling, M., Anderson, K.J., Beecham, G., Berg, D., Biernacka, J.M., Brice, A., DeStefano, A.L., Do, C.B., Eriksson, N., Factor, S.A., Farrer, M.J., Foroud, T., Gasser, T., Hamza, T., Hardy, J.A., Heutink, P., Hill-Burns, E.M., Klein, C., Latourelle, J.C., Maraganore, D.M., Martin, E.R., Martinez, M., Myers, R.H., Nalls, M.A., Pankratz, N., Payami, H., Satake, W., Scott, W.K., Sharma, M., Singleton, A.B., Stefansson, K., Toda, T., Tung, J.Y., Vance, J., Wood, N.W., Zabetian, C.P., Me Genetic Epidemiology of Parkinson's Disease, C., International Parkinson's Disease Genomics, C., Parkinson's Disease, G.C., Wellcome Trust Case Control, C., Young, P., Tanzi, R.E., Khoury, M.J., Zipp, F., Lehrach, H., Ioannidis, J.P., Bertram, L., 2012. Comprehensive Research Synopsis and Systematic Meta-analyses in Parkinson's Disease Genetics: The PDGene database.
Lindersson, E., Beedholm, R., Hojrup, P., Moos, T., Gai, W., Hendil, K.B., Jensen, P.H., 2004. Proteasomal inhibition by alpha-synuclein filaments and oligomers. J. Biol. Chem. 279, 12924–12934.
Liu, X., Cheng, R., Verbitsky, M., Kisselev, S., Browne, A., Mejia-Sanatana, H., Louis, E.D., Cote, L.J., Andrews, H., Waters, C., Ford, B., Frucht, S., Fahn, S., Marder, K., Clark, L.N., Lee, J.H., 2011. Genome-wide association study identifies candidate genes for Parkinson's disease in an Ashkenazi Jewish population. BMC Med. Genet. 12, 104.
Lonser, R.R., Schiffman, R., Robison, R.A., Butman, J.A., Quezado, Z., Walker, M.L., Morrison, P.F., Walbridge, S., Murray, G.J., Park, D.M., Brady, R.O., Oldfield, E.H.,

2007. Image-guided, direct convective delivery of glucocerebrosidase for neuronopathic Gaucher disease. Neurology 68, 254–261.
Lu, J., Yang, C., Chen, M., Ye, D.Y., Lonser, R.R., Brady, R.O., Zhuang, Z., 2011. Histone deacetylase inhibitors prevent the degradation and restore the activity of glucocerebrosidase in Gaucher disease. Proc. Natl. Acad. Sci. U. S. A. 108, 21200–21205.
Luk, K.C., Kehm, V., Carroll, J., Zhang, B., O'Brien, P., Trojanowski, J.Q., Lee, V.M., 2012. Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science 338, 949–953.
Luk, K.C., Song, C., O'Brien, P., Stieber, A., Branch, J.R., Brunden, K.R., Trojanowski, J.Q., Lee, V.M., 2009. Exogenous alpha-synuclein fibrils seed the formation of Lewy body-like intracellular inclusions in cultured cells. Proc. Natl. Acad. Sci. U. S. A. 106, 20051–20056.
Lukina, E., Watman, N., Dragosky, M., Pastores, G.M., Arreguin, E.A., Rosenbaum, H., Zimran, A., Angell, J., Ross, L., Puga, A.C., Peterschmitt, J.M., 2014. Eliglustat, an investigational oral therapy for Gaucher disease type 1: phase 2 trial results after 4years of treatment. Blood Cells. Mol. Dis. 53, 274–276.
Maegawa, G.H., Tropak, M.B., Buttner, J.D., Rigat, B.A., Fuller, M., Pandit, D., Tang, L., Kornhaber, G.J., Hamuro, Y., Clarke, J.T., Mahuran, D.J., 2009. Identification and characterization of ambroxol as an enzyme enhancement agent for Gaucher disease. J. Biol. Chem. 284, 23502–23516.
Manning-Bog, A.B., Schule, B., Langston, J.W., 2009. Alpha-synuclein-glucocerebrosidase interactions in pharmacological Gaucher models: a biological link between Gaucher disease and parkinsonism. Neurotoxicology 30, 1127–1132.
Maor, G., Rencus-Lazar, S., Filocamo, M., Steller, H., Segal, D., Horowitz, M., 2013. Unfolded protein response in Gaucher disease: from human to *Drosophila*. Orphanet J. Rare Dis. 8, 140.
Martinez-Vicente, M., Cuervo, A.M., 2007. Autophagy and neurodegeneration: when the cleaning crew goes on strike. Lancet Neurol. 6, 352–361.
Martinez-Vicente, M., Talloczy, Z., Kaushik, S., Massey, A.C., Mazzulli, J., Mosharov, E.V., Hodara, R., Fredenburg, R., Wu, D.C., Follenzi, A., Dauer, W., Przedborski, S., Ischiropoulos, H., Lansbury, P.T., Sulzer, D., Cuervo, A.M., 2008. Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. J. Clin. Invest. 118, 777–788.
Mazzulli, J.R., Xu, Y.H., Sun, Y., Knight, A.L., McLean, P.J., Caldwell, G.A., Sidransky, E., Grabowski, G.A., Krainc, D., 2011. Gaucher disease glucocerebrosidase and alpha-synuclein form a bidirectional pathogenic loop in synucleinopathies. Cell 146, 37–52.
McNeill, A., Duran, R., Proukakis, C., Bras, J., Hughes, D., Mehta, A., Hardy, J., Wood, N.W., Schapira, A.H., 2012. Hyposmia and cognitive impairment in Gaucher disease patients and carriers. Mov. Disord. 27, 526–532.
McNeill, A., Magalhaes, J., Shen, C., Chau, K.Y., Hughes, D., Mehta, A., Foltynie, T., Cooper, J.M., Abramov, A.Y., Gegg, M., Schapira, A.H., 2014. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain 137, 1481–1495.
Mercado, G., Valdes, P., Hetz, C., 2013. An ERcentric view of Parkinson's disease. Trends Mol. Med. 19, 165–175.
Michelakakis, H., Xiromerisiou, G., Dardiotis, E., Bozi, M., Vassilatis, D., Kountra, P.M., Patramani, G., Moraitou, M., Papadimitriou, D., Stamboulis, E., Stefanis, L., Zintzaras, E., Hadjigeorgiou, G.M., 2012. Evidence of an association between the scavenger receptor class B member 2 gene and Parkinson's disease. Mov. Disord. 27, 400–405.
Mielke, M.M., Maetzler, W., Haughey, N.J., Bandaru, V.V., Savica, R., Deuschle, C., Gasser, T., Hauser, A.K., Graber-Sultan, S., Schleicher, E., Berg, D., Liepelt-Scarfone, I., 2013. Plasma ceramide and glucosylceramide metabolism is altered in sporadic Parkinson's disease and associated with cognitive impairment: a pilot study. PLOS ONE 8, e73094.
Miura, E., Hasegawa, T., Konno, M., Suzuki, M., Sugeno, N., Fujikake, N., Geisler, S., Tabuchi, M., Oshima, R., Kikuchi, A., Baba, T., Wada, K., Nagai, Y., Takeda, A., Aoki, M., 2014. VPS35 dysfunction impairs lysosomal degradation of alpha-synuclein and exacerbates neurotoxicity in a Drosophila model of Parkinson's disease. Neurobiol. Dis. 71C, 1–13.
Murphy, K.E., Gysbers, A.M., Abbott, S.K., Tayebi, N., Kim, W.S., Sidransky, E., Cooper, A., Garner, B., Halliday, G.M., 2014. Reduced glucocerebrosidase is associated with increased alpha-synuclein in sporadic Parkinson's disease. Brain 137, 834–848.
Nalls, M.A., Duran, R., Lopez, G., Kurzawa-Akanbi, M., McKeith, I.G., Chinnery, P.F., Morris, C.M., Theuns, J., Crosiers, D., Cras, P., Engelborghs, S., De Deyn, P.P., Van Broeckhoven, C., Mann, D.M., Snowden, J., Pickering-Brown, S., Halliwell, N., Davidson, Y., Gibbons, L., Harris, J., Sheerin, U.M., Bras, J., Hardy, J., Clark, L., Marder, K., Honig, L.S., Berg, D., Maetzler, W., Brockmann, K., Gasser, T., Novellino, F., Quattrone, A., Annesi, G., De Marco, E.V., Rogaeva, E., Masellis, M., Black, S.E., Bilbao, J.M., Foroud, T., Ghetti, B., Nichols, W.C., Pankratz, N., Halliday, G., Lesage, S., Klebe, S., Durr, A., Duyckaerts, C., Brice, A., Giasson, B.I., Trojanowski, J.Q., Hurtig, H.I., Tayebi, N., Landazabal, C., Knight, M.A., Keller, M., Singleton, A.B., Wolfsberg, T.G., Sidransky, E., 2013. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 70, 727–735.
Nalls, M.A., Pankratz, N., Lill, C.M., Do, C.B., Hernandez, D.G., Saad, M., DeStefano, A.L., Kara, E., Bras, J., Sharma, M., Schulte, C., Keller, M.F., Arepalli, S., Letson, C., Edsall, C., Stefansson, H., Liu, X., Pliner, H., Lee, J.H., Cheng, R., International Parkinson's Disease Genomics Consortium (IPDGC), Parkinson's Study Group (PSG) Parkinson's Research: The Organized GENetics Initiative (PROGENI), 23andMe, GenePD, NeuroGenetics Research Consortium (NGRC), Hussman Institute of Human Genomics (HIHG), Ashkenazi Jewish Dataset Investigator, Cohorts for Health and Aging Research in Genetic Epidemiology (CHARGE), North American Brain Expression Consortium (NABEC), United Kingdom Brain Expression Consortium (UKBEC), Greek Parkinson's Disease Consortium; Alzheimer Genetic Analysis Group, Ikram, M.A., Ioannidis, J.P., Hadjigeorgiou, G.M., Bis, J.C., Martinez, M., Perlmutter, J.S., Goate, A., Marder, K., Fiske, B., Sutherland, M., Xiromerisiou, G., Myers, R.H., Clark, L.N., Stefansson, K., Hardy, J.A., Heutink, P., Chen, H., Wood, N.W., Houlden, H., Payami, H., Brice, A., Scott, W.K., Gasser, T., Bertram, L., Eriksson, N., Foroud, T., Singleton, A.B., 2014. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nat. Genet. 46, 989–993.
Neudorfer, O., Giladi, N., Elstein, D., Abrahamov, A., Turezkite, T., Aghai, E., Reches, A., Bembi, B., Zimran, A., 1996. Occurrence of Parkinson's syndrome in type I Gaucher disease. QJM 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., Segarane, B., Singleton, A., Lees, A., Hardy, J., Houlden, H., Revesz, T., Wood, N.W., 2009. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 132, 1783–1794.
Nichols, W.C., Pankratz, N., Marek, D.K., Pauciulo, M.W., Elsaesser, V.E., Halter, C.A., Rudolph, A., Wojcieszek, J., Pfeiffer, R.F., Foroud, T., 2009. Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. Neurology 72, 310–316.
Nietupski, J.B., Pacheco, J.J., Chuang, W.L., Maratea, K., Li, L., Foley, J., Ashe, K.M., Cooper, C.G., Aerts, J.M., Copeland, D.P., Scheule, R.K., Cheng, S.H., Marshall, J., 2012. Iminosugar-based inhibitors of glucosylceramide synthase prolong survival but paradoxically increase brain glucosylceramide levels in Niemann-Pick C mice. Mol. Genet. Metab. 105, 621–628.
Nilsson, O., Svennerholm, L., 1982. Accumulation of glucosylceramide and glucosylsphingosine (psychosine) in cerebrum and cerebellum in infantile and juvenile Gaucher disease. J. Neurochem. 39, 709–718.
Nixon, R.A., 2013. The role of autophagy in neurodegenerative disease. Nat. Med. 19, 983–997.
Ong, D.S., Mu, T.W., Palmer, A.E., Kelly, J.W., 2010. Endoplasmic reticulum Ca2+ increases enhance mutant glucocerebrosidase proteostasis. Nat. Chem. Biol. 6, 424–432.
Orenstein, S.J., Kuo, S.H., Tasset, I., Arias, E., Koga, H., Fernandez-Carasa, I., Cortes, E., Honig, L.S., Dauer, W., Consiglio, A., Raya, A., Sulzer, D., Cuervo, A.M., 2013. Interplay of LRRK2 with chaperone-mediated autophagy. Nat. Neurosci. 16, 394–406.
Orvisky, E., Park, J.K., LaMarca, M.E., Ginns, E.I., Martin, B.M., Tayebi, N., Sidransky, E., 2002. Glucosylsphingosine accumulation in tissues from patients with Gaucher disease: correlation with phenotype and genotype. Mol. Genet. Metab. 76, 262–270.
Osellame, L.D., Rahim, A.A., Hargreaves, I.P., Gegg, M.E., Richard-Londt, A., Brandner, S., Waddington, S.N., Schapira, A.H., Duchen, M.R., 2013. Mitochondria and quality control defects in a mouse model of Gaucher disease – links to Parkinson's disease. Cell Metab. 17, 941–953.
Parkinson, J., 1817. An Essay on the Shaking Palsy.
Parnetti, L., Chiasserini, D., Persichetti, E., Eusebi, P., Varghese, S., Qureshi, M.M., Dardis, A., Deganuto, M., De Carlo, C., Castrioto, A., Balducci, C., Paciotti, S., Tambasco, N., Bembi, B., Bonanni, L., Onofrj, M., Rossi, A., Beccari, T., El-Agnaf, O., Calabresi, P., 2014. Cerebrospinal fluid lysosomal enzymes and alpha-synuclein in Parkinson's disease. Mov. Disord. 29, 1019–1027.
Passini, M.A., Bu, J., Richards, A.M., Treleaven, C.M., Sullivan, J.A., O'Riordan, C.R., Scaria, A., Kells, A.P., Samaranch, L., San Sebastian, W., Federici, T., Fiandaca, M.S., Boulis, N.M., Bankiewicz, K.S., Shihabuddin, L.S., Cheng, S.H., 2014. Translational fidelity of intrathecal delivery of self-complementary AAV9-survival motor neuron 1 for spinal muscular atrophy. Hum. Gene Ther. 25, 619–630.
Pastores, G.M., 2010. Recombinant glucocerebrosidase (imiglucerase) as a therapy for Gaucher disease. BioDrugs 24, 41–47.
Patnaik, S., Zheng, W., Choi, J.H., Motabar, O., Southall, N., Westbroek, W., Lea, W.A., Velayati, A., Goldin, E., Sidransky, E., Leister, W., Marugan, J.J., 2012. Discovery, structure-activity relationship, and biological evaluation of noninhibitory small molecule chaperones of glucocerebrosidase. J. Med. Chem. 55, 5734–5748.
Pchelina, S.N., Nuzhnyi, E.P., Emelyanov, A.K., Boukina, T.M., Usenko, T.S., Nikolaev, M.A., Salogub, G.N., Yakimovskii, A.F., Zakharova, E.Y., 2014. Increased plasma oligomeric alpha-synuclein in patients with lysosomal storage diseases. Neurosci. Lett. 583, 188–193.
Polymeropoulos, M.H., Lavedan, C., Leroy, E., Ide, S.E., Dehejia, A., Dutra, A., Pike, B., Root, H., Rubenstein, J., Boyer, R., Stenroos, E.S., Chandrasekharappa, S., Athanassiadou, A., Papapetropoulos, T., Johnson, W.G., Lazzarini, A.M., Duvoisin, R.C., Di Iorio, G., Golbe, L.I., Nussbaum, R.L., 1997. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 276, 2045–2047.
Poole, R.M., 2014. Eliglustat: first global approval. Drugs 74, 1829–1836.
Re, D.B., Le Verche, V., Yu, C., Amoroso, M.W., Politi, K.A., Phani, S., Ikiz, B., Hoffmann, L., Koolen, M., Nagata, T., Papadimitriou, D., Nagy, P., Mitsumoto, H., Kariya, S., Wichterle, H., Henderson, C.E., Przedborski, S., 2014. Necroptosis drives motor neuron death in models of both sporadic and familial ALS. Neuron 81, 1001–1008.
Reczek, D., Schwake, M., Schroder, J., Hughes, H., Blanz, J., Jin, X., Brondyk, W., Van Patten, S., Edmunds, T., Saftig, P., 2007. LIMP-2 is a receptor for lysosomal mannose-6-phosphate-independent targeting of beta-glucocerebrosidase. Cell 131, 770–783.
Richter, F., Fleming, S.M., Watson, M., Lemesre, V., Pellegrino, L., Ranes, B., Zhu, C., Mortazavi, F., Mulligan, C.K., Sioshansi, P.C., Hean, S., De La Rosa, K., Khanna, R., Flanagan, J., Lockhart, D.J., Wustman, B.A., Clark, S.W., Chesselet, M.F., 2014. A GCase chaperone improves motor function in a mouse model of synucleinopathy. Neurotherapeutics 11, 840–856.

Rogaeva, E., Hardy, J., 2008. Gaucher and Parkinson diseases: unexpectedly related. Neurology 70, 2272–2273.

Rogers, S., Patnaik, S., Schoenen, F., Zheng, W., Choi, J., Motabar, O., Southall, N., Westbroek, W., Goldin, E., Sidransky, E., Leister, W., Marugan, J.J., Aube, J., 2012. Discovery, SAR, and biological evaluation of non-inhibitory chaperones of glucocerebrosidaseIn: Probe Reports from the NIH Molecular Libraries Program: Bethesda (MD). .

Ron, I., Horowitz, M., 2005. ER retention and degradation as the molecular basis underlying Gaucher disease heterogeneity. Hum. Mol. Genet. 14, 2387–2398.

Ron, I., Rapaport, D., Horowitz, M., 2010. Interaction between parkin and mutant glucocerebrosidase variants: a possible link between Parkinson disease and Gaucher disease. Hum. Mol. Genet. 19, 3771–3781.

Rosenbloom, B., Balwani, M., Bronstein, J.M., Kolodny, E., Sathe, S., Gwosdow, A.R., Taylor, J.S., Cole, J.A., Zimran, A., Weinreb, N.J., 2011. The incidence of Parkinsonism in patients with type 1 Gaucher disease: data from the ICGG Gaucher Registry. Blood Cells. Mol. Dis. 46, 95–102.

Rothaug, M., Zunke, F., Mazzulli, J.R., Schweizer, M., Altmeppen, H., Lullmann-Rauch, R., Kallemeijn, W.W., Gaspar, P., Aerts, J.M., Glatzel, M., Saftig, P., Krainc, D., Schwake, M., Blanz, J., 2014. LIMP-2 expression is critical for beta-glucocerebrosidase activity and alpha-synuclein clearance. Proc. Natl. Acad. Sci. U. S. A. 111, 15573–15578.

Sardi, S.P., Clarke, J., Kinnecom, C., Tamsett, T.J., Li, L., Stanek, L.M., Passini, M.A., Grabowski, G.A., Schlossmacher, M.G., Sidman, R.L., Cheng, S.H., Shihabuddin, L.S., 2011. CNS expression of glucocerebrosidase corrects alpha-synuclein pathology and memory in a mouse model of Gaucher-related synucleinopathy. Proc. Natl. Acad. Sci. U S A 108, 12101–12106.

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., Yu, W.H., Sidman, R.L., Cheng, S.H., Shihabuddin, L.S., 2013. Augmenting CNS glucocerebrosidase activity as a therapeutic strategy for parkinsonism and other Gaucher-related synucleinopathies. Proc. Natl. Acad. Sci. U. S. A. 110, 3537–3542.

Sardi, S.P., Singh, P., Cheng, S.H., Shihabuddin, L.S., Schlossmacher, M.G., 2012. Mutant GBA1 expression and synucleinopathy risk: first insights from cellular and mouse models. Neurodegener. Dis. 10, 195–202.

Sardiello, M., Palmieri, M., di Ronza, A., Medina, D.L., Valenza, M., Gennarino, V.A., Di Malta, C., Donaudy, F., Embrione, V., Polishchuk, R.S., Banfi, S., Parenti, G., Cattaneo, E., Ballabio, A., 2009. A gene network regulating lysosomal biogenesis and function. Science 325, 473–477.

Schlossmacher, M., 2007. α-synuclein and synucleinopathies. In: Growdon, J.H., Rossor, M.N. (Eds.), The Dementias 2. Butterworth Heinemann, Inc., Oxford, pp. 186–215.

Schondorf, D.C., Aureli, M., McAllister, F.E., Hindley, C.J., Mayer, F., Schmid, B., Sardi, S.P., Valsecchi, M., Hoffmann, S., Schwarz, L.K., Hedrich, U., Berg, D., Shihabuddin, L.S., Hu, J., Pruszak, J., Gygi, S.P., Sonnino, S., Gasser, T., Deleidi, M., 2014. iPSC-derived neurons from GBA1-associated Parkinson's disease patients show autophagic defects and impaired calcium homeostasis. Nat. Commun. 5, 4028.

Segarane, B., Li, A., Paudel, R., Scholz, S., Neumann, J., Lees, A., Revesz, T., Hardy, J., Mathias, C.J., Wood, N.W., Holton, J., Houlden, H., 2009. Glucocerebrosidase mutations in 108 neuropathologically confirmed cases of multiple system atrophy. Neurology 72, 1185–1186.

Seto-Salvia, N., Pagonabarraga, J., Houlden, H., Pascual-Sedano, B., Dols-Icardo, O., Tucci, A., Paisan-Ruiz, C., Campolongo, A., Anton-Aguirre, S., Martin, I., Munoz, L., Bufill, E., Vilageliu, L., Grinberg, D., Cozar, M., Blesa, R., Lleo, A., Hardy, J., Kulisevsky, J., Clarimon, J., 2012. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov. Disord. 27, 393–399.

Settembre, C., Fraldi, A., Medina, D.L., Ballabio, A., 2013. Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat. Rev. Mol. Cell Biol. 14, 283–296.

Shen, W., Henry, A.G., Paumier, K.L., Li, L., Mou, K., Dunlop, J., Berger, Z., Hirst, W.D., 2014. Inhibition of glucosylceramide synthase stimulates autophagy flux in neurons. J. Neurochem. 129, 884–894.

Sidransky, E., 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., Chen, C.M., Clark, L.N., Condroyer, C., De Marco, E.V., Durr, A., Eblan, M.J., Fahn, S., Farrer, M.J., Fung, H.C., Gan-Or, Z., Gasser, T., Gershoni-Baruch, R., Giladi, N., Griffith, A., Gurevich, T., Januario, C., Kropp, P., Lang, A.E., Lee-Chen, G.J., Lesage, S., Marder, K., Mata, I.F., Mirelman, A., Mitsui, J., Mizuta, I., Nicoletti, G., Oliveira, C., Ottman, R., Orr-Urtreger, A., Pereira, L.V., Quattrone, A., Rogaeva, E., Rolfs, A., Rosenbaum, H., Rozenberg, R., Samii, A., Samaddar, T., Schulte, C., Sharma, M., Singleton, A., Spitz, M., Tan, E.K., Tayebi, N., Toda, T., Troiano, A.R., Tsuji, S., Wittstock, M., Wolfsberg, T.G., Wu, Y.R., Zabetian, C.P., Zhao, Y., Ziegler, S.G., 2009. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N. Engl. J. Med. 361, 1651–1661.

Sorge, J.A., West, C., Kuhl, W., Treger, L., Beutler, E., 1987. The human glucocerebrosidase gene has two functional ATG initiator codons. Am. J. Hum. Genet. 41, 1016–1024.

Spencer, B., Potkar, R., Trejo, M., Rockenstein, E., Patrick, C., Gindi, R., Adame, A., Wyss-Coray, T., Masliah, E., 2009. Beclin 1 gene transfer activates autophagy and ameliorates the neurodegenerative pathology in alpha-synuclein models of Parkinson's and Lewy body diseases. J. Neurosci. 29, 13578–13588.

Spencer, B.J., Verma, I.M., 2007. Targeted delivery of proteins across the blood–brain barrier. Proc. Natl. Acad. Sci. U. S. A. 104, 7594–7599.

Spillantini, M.G., Schmidt, M.L., Lee, V.M., Trojanowski, J.Q., Jakes, R., Goedert, M., 1997. Alpha-synuclein in Lewy bodies. Nature 388, 839–840.

Srulijes, K., Hauser, A.K., Guella, I., Asselta, R., Brockmann, K., Schulte, C., Solda, G., Cilia, R., Maetzler, W., Schols, L., Wenning, G.K., Poewe, W., Barone, P., Wullner, U., Oertel, W., Berg, D., Goldwurm, S., Gasser, T., 2013. No association of GBA mutations and multiple system atrophy. Eur. J. Neurol 20, e61–e62.

Stefanis, L., 2012. α-Synuclein in Parkinson's disease. Cold Spring Harb. Perspect. Med. 2, a009399.

Tamargo, R.J., Velayati, A., Goldin, E., Sidransky, E., 2012. The role of saposin C in Gaucher disease. Mol. Genet. Metab. 106, 257–263.

Tan, Y.L., Genereux, J.C., Pankow, S., Aerts, J.M., Yates 3rd, J.R., Kelly, J.W., 2014. ERdj3 is an endoplasmic reticulum degradation factor for mutant glucocerebrosidase variants linked to Gaucher's disease. Chem. Biol. 21, 967–976.

Thayanidhi, N., Helm, J.R., Nycz, D.C., Bentley, M., Liang, Y., Hay, J.C., 2010. Alpha-synuclein delays endoplasmic reticulum (ER)-to-Golgi transport in mammalian cells by antagonizing ER/Golgi SNAREs. Mol. Biol. Cell 21, 1850–1863.

Tofaris, G.K., 2012. Lysosome-dependent pathways as a unifying theme in Parkinson's disease. Mov. Disord. 27, 1364–1369.

Trapero, A., Llebaria, A., 2013. Glucocerebrosidase inhibitors for the treatment of Gaucher disease. Future Med. Chem. 5, 573–590.

Tsika, E., Glauser, L., Moser, R., Fiser, A., Daniel, G., Sheerin, U.M., Lees, A., Troncoso, J.C., Lewis, P.A., Bandopadhyay, R., Schneider, B.L., Moore, D.J., 2014. Parkinson's disease-linked mutations in VPS35 induce dopaminergic neurodegeneration. Hum. Mol. Genet. 23, 4621–4638.

Tsunemi, T., Ashe, T.D., Morrison, B.E., Soriano, K.R., Au, J., Roque, R.A., Lazarowski, E.R., Damian, V.A., Masliah, E., La Spada, A.R., 2012. PGC-1alpha rescues Huntington's disease proteotoxicity by preventing oxidative stress and promoting TFEB function. Sci. Transl. Med. 4 (142), ra197.

Usenovic, M., Tresse, E., Mazzulli, J.R., Taylor, J.P., Krainc, D., 2012. Deficiency of ATP13A2 leads to lysosomal dysfunction, alpha-synuclein accumulation, and neurotoxicity. J. Neurosci. 32, 4240–4246.

Vacic, V., Ozelius, L.J., Clark, L.N., Bar-Shira, A., Gana-Weisz, M., Gurevich, T., Gusev, A., Kedmi, M., Kenny, E.E., Liu, X., Mejia-Santana, H., Mirelman, A., Raymond, D., Saunders-Pullman, R., Desnick, R.J., Atzmon, G., Burns, E.R., Ostrer, H., Hakonarson, H., Bergman, A., Barzilai, N., Darvasi, A., Peter, I., Guha, S., Lencz, T., Giladi, N., Marder, K., Pe'er, I., Bressman, S.B., Orr-Urtreger, A., 2014. Genome-wide mapping of IBD segments in an Ashkenazi PD cohort identifies associated haplotypes. Hum. Mol. Genet. 23, 4693–4702.

Vandenabeele, P., Galluzzi, L., Vanden Berghe, T., Kroemer, G., 2010. Molecular mechanisms of necroptosis: an ordered cellular explosion. Nat. Rev. Mol. Cell Biol. 11, 700–714.

Vekrellis, K., Xilouri, M., Emmanouilidou, E., Rideout, H.J., Stefanis, L., 2011. Pathological roles of alpha-synuclein in neurological disorders. Lancet Neurol. 10, 1015–1025.

Velayati, A., Yu, W.H., Sidransky, E., 2010. The role of glucocerebrosidase mutations in Parkinson disease and Lewy body disorders. Curr. Neurol. Neurosci. Rep. 10, 190–198.

Vilarino-Guell, C., Wider, C., Ross, O.A., Dachsel, J.C., Kachergus, J.M., Lincoln, S.J., Soto-Ortolaza, A.I., Cobb, S.A., Wilhoite, G.J., Bacon, J.A., Behrouz, B., Melrose, H.L., Hentati, E., Puschmann, A., Evans, D.M., Conibear, E., Wasserman, W.W., Aasly, J.O., Burkhard, P.R., Djaldetti, R., Ghika, J., Hentati, F., Krygowska-Wajs, A., Lynch, T., Melamed, E., Rajput, A., Rajput, A.H., Solida, A., Wu, R.M., Uitti, R.J., Wszolek, Z.K., Vingerhoets, F., Farrer, M.J., 2011. VPS35 mutations in Parkinson disease. Am. J. Hum. Genet. 89, 162–167.

Vitner, E.B., Salomon, R., Farfel-Becker, T., Meshcheriakova, A., Ali, M., Klein, A.D., Platt, F.M., Cox, T.M., Futerman, A.H., 2014. RIPK3 as a potential therapeutic target for Gaucher's disease. Nat. Med. 20, 204–208.

Wang, C., Cai, Y., Gu, Z., Ma, J., Zheng, Z., Tang, B.S., Xu, Y., Zhou, Y., Feng, T., Wang, T., Chen, S.D., Chan, P., Chinese Parkinson Study Group, 2014. Clinical profiles of Parkinson's disease associated with common leucine-rich repeat kinase 2 and glucocerebrosidase genetic variants in Chinese individuals. Neurobiol. Aging 35, e721–e726.

Wang, F., Segatori, L., 2013. Remodeling the proteostasis network to rescue glucocerebrosidase variants by inhibiting ER-associated degradation and enhancing ER folding. PLoS ONE 8, e61418.

Wang, W., Perovic, I., Chittuluru, J., Kaganovich, A., Nguyen, L.T., Liao, J., Auclair, J.R., Johnson, D., Landeru, A., Simorellis, A.K., Ju, S., Cookson, M.R., Asturias, F.J., Agar, J.N., Webb, B.N., Kang, C., Ringe, D., Petsko, G.A., Pochapsky, T.C., Hoang, Q.Q., 2011. A soluble alpha-synuclein construct forms a dynamic tetramer. Proc. Natl. Acad. Sci. U. S. A. 108, 17797–17802.

Watts, R.J., Dennis, M.S., 2013. Bispecific antibodies for delivery into the brain. Curr. Opin. Chem. Biol. 17, 393–399.

Winder-Rhodes, S.E., Evans, J.R., Ban, M., Mason, S.L., Williams-Gray, C.H., Foltynie, T., Duran, R., Mencacci, N.E., Sawcer, S.J., Barker, R.A., 2013. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 136, 392–399.

Winfield, S.L., Tayebi, N., Martin, B.M., Ginns, E.I., Sidransky, E., 1997. Identification of three additional genes contiguous to the glucocerebrosidase locus on chromosome 1q21: implications for Gaucher disease. Genome Res. 7, 1020–1026.

Wong, K., Sidransky, E., Verma, A., Mixon, T., Sandberg, G.D., Wakefield, L.K., Morrison, A., Lwin, A., Colegial, C., Allman, J.M., Schiffmann, R., 2004. Neuropathology provides clues to the pathophysiology of Gaucher disease. Mol. Genet. Metab. 82, 192–207.

Woodard, Chris, M., Campos, Brian, A., Kuo, S.-H., Nirenberg, Melissa, J., Nestor, Michael, W., Zimmer, M., Mosharov, E.V., Sulzer, D., Zhou, H., Paull, D., Clark, L., Schadt, Eric, E., Sardi, Sergio, P., Rubin, L., Eggan, K., Brock, M., Lipnick, S., Rao, M., Chang, S., Li, A., Noggle, Scott, A., 2014. iPSC-derived dopamine neurons reveal

differences between monozygotic twins discordant for Parkinson's Disease. Cell Rep. 9, 1173–1182.
Xilouri, M., Brekk, O.R., Landeck, N., Pitychoutis, P.M., Papasilekas, T., Papadopoulou-Daifoti, Z., Kirik, D., Stefanis, L., 2013. Boosting chaperone-mediated autophagy in vivo mitigates alpha-synuclein-induced neurodegeneration. Brain 136, 2130–2146.
Xu, Y.H., Sun, Y., Ran, H., Quinn, B., Witte, D., Grabowski, G.A., 2010. Accumulation and distribution of alpha-synuclein and ubiquitin in the CNS of Gaucher disease mouse models. Mol. Genet. Metab. 102, 436–447.
Xu, Y.H., Xu, K., Sun, Y., Liou, B., Quinn, B., Li, R.H., Xue, L., Zhang, W., Setchell, K.D., Witte, D., Grabowski, G.A., 2014. Multiple pathogenic proteins implicated in neuronopathic Gaucher disease mice. Hum. Mol. Genet. 23, 3943–3957.
Yang, B., Li, S., Wang, H., Guo, Y., Gessler, D.J., Cao, C., Su, Q., Kramer, J., Zhong, L., Ahmed, S.S., Zhang, H., He, R., Desrosiers, R.C., Brown, R., Xu, Z., Gao, G., 2014a. Global CNS transduction of adult mice by intravenously delivered rAAVrh.8 and rAAVrh.10 and nonhuman primates by rAAVrh.10. Mol. Ther. 22, 1299–1309.
Yang, C., Rahimpour, S., Lu, J., Pacak, K., Ikejiri, B., Brady, R.O., Zhuang, Z., 2013. Histone deacetylase inhibitors increase glucocerebrosidase activity in Gaucher disease by modulation of molecular chaperones. Proc. Natl. Acad. Sci. U. S. A. 110, 966–971.
Yang, C., Swallows, C.L., Zhang, C., Lu, J., Xiao, H., Brady, R.O., Zhuang, Z., 2014b. Celastrol increases glucocerebrosidase activity in Gaucher disease by modulating molecular chaperones. Proc. Natl. Acad. Sci. U. S. A. 111, 249–254.
Yap, T.L., Gruschus, J.M., Velayati, A., Sidransky, E., Lee, J.C., 2013a. Saposin C protects glucocerebrosidase against alpha-synuclein inhibition. Biochemistry 52, 7161–7163.
Yap, T.L., Gruschus, J.M., Velayati, A., Westbroek, W., Goldin, E., Moaven, N., Sidransky, E., Lee, J.C., 2011. Alpha-synuclein interacts with glucocerebrosidase providing a molecular link between Parkinson and Gaucher diseases. J. Biol. Chem. 286, 28080–28088.
Yap, T.L., Velayati, A., Sidransky, E., Lee, J.C., 2013b. Membrane-bound alpha-synuclein interacts with glucocerebrosidase and inhibits enzyme activity. Mol. Genet. Metab. 108, 56–64.
Zavodszky, E., Seaman, M.N., Moreau, K., Jimenez-Sanchez, M., Breusegem, S.Y., Harbour, M.E., Rubinsztein, D.C., 2014. Mutation in VPS35 associated with Parkinson's disease impairs WASH complex association and inhibits autophagy. Nat. Commun. 5, 3828.
Ziegler, R.J., Salegio, E.A., Dodge, J.C., Bringas, J., Treleaven, C.M., Bercury, S.D., Tamsett, T.J., Shihabuddin, L., Hadaczek, P., Fiandaca, M., Bankiewicz, K., Scheule, R.K., 2011. Distribution of acid sphingomyelinase in rodent and non-human primate brain after intracerebroventricular infusion. Exp. Neurol. 231, 261–271.
Zimprich, A., Benet-Pages, A., Struhal, W., Graf, E., Eck, S.H., Offman, M.N., Haubenberger, D., Spielberger, S., Schulte, E.C., Lichtner, P., Rossle, S.C., Klopp, N., Wolf, E., Seppi, K., Pirker, W., Presslauer, S., Mollenhauer, B., Katzenschlager, R., Foki, T., Hotzy, C., Reinthaler, E., Harutyunyan, A., Kralovics, R., Peters, A., Zimprich, F., Brucke, T., Poewe, W., Auff, E., Trenkwalder, C., Rost, B., Ransmayr, G., Winkelmann, J., Meitinger, T., Strom, T.M., 2011. A mutation in VPS35, encoding a subunit of the retromer complex, causes late-onset Parkinson disease. Am. J. Hum. Genet. 89, 168–175.
Zimran, A., Altarescu, G., Elstein, D., 2013. Pilot study using ambroxol as a pharmacological chaperone in type 1 Gaucher disease. Blood Cells. Mol. Dis. 50, 134–137.
Zokaei, N., McNeill, A., Proukakis, C., Beavan, M., Jarman, P., Korlipara, P., Hughes, D., Mehta, A., Hu, M.T., Schapira, A.H., Husain, M., 2014. Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain 137, 2303–2311.