

Glucocerebrosidase and Parkinson disease: molecular, clinical and therapeutic implications.

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Introduction

2017 represents the 200th anniversary of the publication of *The Shaking Palsy* by James Parkinson and the 20th anniversary of the discovery of the first unequivocal cause of Parkinson disease (PD) – a mutation in the α -synuclein gene (Polymeropoulos et al. 1997). These two anniversaries reflect the accelerating pace of progress in understanding the causes of and developing new treatments for this and other neurodegenerative diseases, particularly given that over 20 Parkinson-related genes have been described just in the last 20 years. This review focuses on a recent and exciting observation that mutations in the glucocerebrosidase (GBA) gene are the most common genetic association with PD and dementia with Lewy bodies. We have attempted to provide a brief overview of clinical features, epidemiology and pathology of PD in order to provide a background to provide a detailed review of the contribution of GBA gene mutations to PD and how our understanding of this relationship is providing invaluable insights into the design of novel therapies that might be used to slow the progress of PD.

PD: CLINICAL OVERVIEW

PD is a complex neurodegenerative disease characterised by a broad range of motor and non-motor features (Table 1).

Motor features

The cardinal motor symptoms are tremor, bradykinesia/hypokinesia/akinesia, rigidity and postural instability.

The majority of PD patients develop tremor; 4-6 Hz rest tremor is the most common and characteristic form of tremor in PD, it is usually unilateral or at least asymmetrical and more evident in the distal extremities of limbs, but it can also occur in the lips, chin, jaw and legs. Other types of tremor such as postural ("re-emergent") or kinetic tremor can be detected. Sometimes patients refer an "internal tremor", which is not detectable with neurological examination.

Bradykinesia, hypokinesia and akinesia are commonly used synonymously, even though they refer to different disturbances of voluntary movement execution and they don't always coexist in individual patients. Bradykinesia can simplistically be defined as slowness in movements (especially repetitive ones) with progressive reduction in amplitude and speed, with the loss of the fluidity of voluntary movements - although PD patients can show difficulties not only in executing but also in planning and initiating movement.

Rigidity refers to an increased resistance to passive movements, due to a continuous and uniform increase in muscle tone. Two types of parkinsonian rigidity are classically recognized: the "lead pipe" rigidity, which is uniform throughout range of movement and is not dependent on passive movement velocity, and the "cog-wheel" rigidity, in which the rigidity is regularly interrupted by tremor during passive movements.

Rigidity must be differentiated from other forms of hypertonia, such as spasticity and paratonia.

Postural instability usually occurs in the later stages of the disease; it is one of the strongest determinants of quality of life, disability and risk of falls and fractures, and consequently morbidity and mortality, in PD.

Postural instability is determined by different causes such as: impaired postural reflexes, lack of control of voluntary movements, orthostatic hypotension, age related sensory changes and weakening of leg

muscles and dyskinesias and other parkinsonian symptoms.

PD is characterised by other motor features, such as postural abnormalities (camptocormia and Pisa syndrome), freezing of gait, festination, micrographia, hypomimia, alteration of blinking and eye movements and others.

Non-motor features

Even if motor symptoms have historically been recognised as the defining features of PD, non-motor symptoms (NMS) are an integral part of the clinical picture (Chaudhuri et al. 2006; Schapira et al. 2017). NMS in PD cover a wide variety of manifestations, including autonomic, gastro-intestinal, sleep, sensory, cognitive, and neuropsychiatric disturbances, disturbances of speech, dysphagia and sialorrhoea; their frequency and/or severity usually increase in later stages of the disease, but they can also appear in early stages. NMS may be misdiagnosed, but when properly assessed they are found to affect the majority of PD patients and have a severe impact on health-related quality of life and disability. Some NMS might arise before the emergence of motor symptoms: depression, constipation and rapid eye movement behaviour sleep disorder (RBD) can precede PD diagnosis and are therefore called “prodromal” or “premotor” symptoms.

EPIDEMIOLOGY AND RISK FACTORS

PD is the second most common neurodegenerative disease in the general population (de Rijk et al. 1997). In industrialised countries, its prevalence is estimated to be 0.3 % in the general population and to be 3 fold and 10 fold higher in the over-60 and over-80 year old populations respectively. The incidence rates range between 8 and 18 per 100,000 person-year, rising up to 121 cases/100,000 person-years in people aged 40-85 and 200-per 100,000 in people aged 60-84 years (Lee and Gilbert 2016). Age is considered to

be the most important risk factor for PD. Men have a higher risk of developing PD, have an earlier onset and show different clinical features (Gillies et al. 2014). Different risk/protective factors have been linked to PD: their mechanism of action will be further explained in specific sections of this article. Risk factors include pesticides, herbicides, insecticides, fungicides or paraquat exposure, rural living, farming and well-water consumption (Breckenridge et al. 2016); exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and annonacin have been found as causative factors in two particular forms of parkinsonism (Langston and Palfreman 1996; Champy et al. 2004). Protective factors include caffeine consumption, cigarette smoking, use of calcium channel blockers and statins, while contrasting evidence is available regarding use of NSAIDS, uric acid levels or gout (Kalia and Lang 2015).

PATHOLOGY

Loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) with the accumulation of α -synuclein in Lewy bodies (LB) and Lewy neurites are the pathological hallmarks of PD (Fig.1a). It is suggested that at the time of motor symptoms and diagnosis dopaminergic neurons in the SNc are reduced up to 60% (Marsden 1990). LB are composed of more than 90 different proteins, of which the most abundant is α -synuclein (Spillantini et al. 1997; Wakabayashi et al. 2013). Besides the SNc, LB are widely distributed in different structures of the central nervous system; it has been proposed that LB and α -synuclein accumulation follow a sequential pattern of deposition, starting in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus and progressively spread to the brain stem. In later stages, the involvement spreads to the cortex, firstly to the mesocortex and allocortex and finally to the neocortex (Fig.1b) (Braak et al. 2003) .

α -synuclein pathology in PD has been found in structures other than the brain: LB-like aggregates have been found in the olfactory epithelium, in dorsal root ganglia, cranial and spinal nerves, in the enteric

nervous system, the adrenal gland, in skin nerves and other structures; however, LB-like structures are also found in peripheral structures in healthy elderly subjects (Longhena et al. 2017).

The deposition of LB and α -synuclein is accompanied by microglial activation and elevation of inflammatory cytokines levels, suggesting that inflammation could contribute to neurodegeneration: a current hypothesis is that there is a positive feedback loop between microglia activation, neuroinflammation and α -synuclein deposition which contributes to neurodegeneration (Zhang et al. 2017).

PATHOGENESIS

α -synuclein

α -synuclein is a 140 amino acid presynaptic protein, whose main role is thought related to neurotransmitter release through the SNARE complex (Burré et al. 2010). The pathogenicity of α -synuclein seems to be related to its accumulation, misfolding and aggregation more than a loss of function. Knockout or depletion of the α -synuclein gene (SNCA) in animal models do not cause a parkinsonian phenotype (Abeliovich et al. 2000), although there is an impairment in vesicle trafficking (Murphy et al. 2000); SNCA knock-out has been shown to be protective against PD-related neurodegeneration (Luk et al. 2012).

The pathogenicity of α -synuclein relies on its tendency to misfold and accumulate. In its native state, α -synuclein is a folded tetramer of 58 kDa (Bartels et al. 2011; Wang et al. 2011), but it can acquire oligomeric and aggregated conformations, which are the most abundant forms in LB. The accumulation and aggregation of α -synuclein is a stepwise process: misfolded monomers aggregate firstly into dimers and then in oligomers that are stabilized by beta-sheet-like interactions; these aggregates become insoluble protofibrils and finally amyloid-like structures.

The oligomeric and protofibrillar forms are considered more toxic than the β -sheet-rich amyloid

aggregate, their toxicity is mediated through a number of mechanisms including mitochondrial (Hsu et al. 2000), lysosomal (Chu et al. 2009) and proteasomal (Snyder et al. 2003) dysfunction, damage to biological membranes (Danzer et al. 2007) and the cytoskeleton (Alim et al. 2004) and the disruption of synaptic function (Scott et al. 2010). It has been suggested that LB may represent an attempt to limit the toxicity of these forms, thereby constituting a neuroprotective factor and an epiphenomenon to neurodegeneration more than a factor contributing to it (Ding et al. 2002; Lashuel, Hartley, et al. 2002; Lashuel, Petre, et al. 2002).

The first insight to the role of α -synuclein in the pathogenesis of PD came from the discovery of its mutation (A53T) in an autosomal dominant form of PD (Polymeropoulos et al. 1997): this mutation, results in more rapid oligomerization than the wild-type (Conway et al. 2000); other pathogenic mutations of SNCA affect the quantity of α -synuclein, such as duplications (Chartier-Harlin et al. 2004; Ibáñez et al. 2004), triplications (Singleton et al. 2003), and mutations in promoter regions (Pals et al. 2004); moreover, higher levels of α -synuclein mRNA have been found in sporadic PD (Chiba-Falek et al. 2006). However, it's not only the production of α -synuclein that determines its accumulation: other mechanisms, such as changes in its turnover via the ubiquitination-proteasome pathway and autophagy, can contribute -as will be discussed in the following section of this review. Oligomeric or fibrillar α -synuclein has the ability to spread to other cells: it was found in grafted neurons in the brains of PD patients that had received fetal implants; this finding was reproduced in vitro and in vivo and then α -synuclein has been demonstrated to spread also when inoculated in the absence of other pathogenic circumstances (Brundin et al. 2016).

ENDOPLASMIC RETICULUM STRESS

The accumulation of misfolded proteins in the cell leads to a condition known as endoplasmic reticulum (ER) stress: when misfolded proteins accumulate in the ER, a feedback mechanism up-regulates the

transcription of chaperones and other stress-induced proteins; this process is called unfolded protein response (UPR) and in both physiological and pathological conditions, it maintains the homeostasis of the ER and recycles the unfolded proteins through ER-associated degradation (ERAD): misfolded or unassembled polypeptides are retro-translocated into the cytosol for degradation by the ubiquitin proteasomal or lysosomal systems (Zhang and Ye 2014); however, if the misfolded protein load and ER stress are irreversible, the apoptosis pathway is activated (Hetz 2012). As well for other neurodegenerative diseases (Matus et al. 2011), an increase in ER stress is thought to be linked with PD pathogenesis: ER stress markers (Colla, Coune, et al. 2012) together with α -synuclein deposition in the ER (Colla, Jensen, et al. 2012) have been found both in in-vivo and autoptical studies (Hoozemans et al. 2007). One of the genes implicated in PD pathogenesis plays a regulatory role in ER stress and associated neurodegeneration (Yuan et al. 2011): mutations in LRRK2 cause a familial form of PD, characterized by relatively late onset, variable penetrance and pleomorphic pathological features (Funayama et al. 2002). The physiological role of this protein is still debated, and may include protection of the cell in the case of ER stress (Dächsel et al. 2010).

DISTURBANCES OF AUTOPHAGY AND LYSOSOMAL FUNCTION

There is increasing evidence that defects in autophagy and lysosomal pathways play a key role in the pathogenesis of PD.

Autophagy is a process that allows the cell to degrade and recycle, through the lysosomes, cytosolic molecules or organelles. It is enhanced in response to cell injury, starvation or hormonal signalling; alternatively, autophagy can prime cell death. Three different kind of autophagy are known: microautophagy, macroautophagy and chaperone-mediated autophagy; even though the three pathways are distinct, they all culminate in the lysosome (Galluzzi et al. 2017). In macro-autophagy (autophagy) the

cargo to be directed to the lysosome is transported in a double-membrane vesicle (autophagosome). The autophagosome then fuses its membrane with the lysosome forming the autolysosome or, in case of convergence with the endocytic pathway, an amphisome; after degradation, all the products of this process are transferred back to the cytosol to be recycled for energy production or biosynthesis of cell components. The term microautophagy refers to a process where cytosolic molecules are sequestered directly by the lysosomal membrane into intra-lysosomal vesicles, it is constitutively active and regulates the turnover cell components; however, the details about the regulation of this mechanism still have to be outlined. In chaperone-mediated autophagy (CMA), proteins that are “marked” by a specific peptide sequence (KFERQ-like) are transported to the lysosome by a cytosolic chaperone (HSC70) through a receptor in the lysosomal membrane, the lysosome-associated membrane protein (LAMP) type 2A.

Besides of alterations in α -synuclein production and folding, disturbances in its degradation and/or clearance can determine its accumulations (Cuervo et al. 2004). Wild-type α -synuclein is degraded by both by autophagy and by the CMA pathway; it contains the pentapeptide sequence $_{95}\text{VKKDQ}_{99}$, which is recognised by the CMA pathway as well as by the proteasome (Webb et al. 2003)(Webb, Ravikumar, Atkins, Skepper, and Rubinsztein 2003)(Webb et al. 2003). Upregulation or inhibition of autophagy processes respectively decrease or increase the level of α -synuclein in cells. In contrast, mutant (A30P and A53T) α -synuclein are not only not efficiently degraded by this pathway, but inhibit it, with toxic consequences for the cell.

LRKK2 has been implicated in this network: physiologically, LRKK2 is degraded by CMA; the degradation of mutated forms interferes with CMA, as mutant LRRK2 blocks LAMP-2A oligomerization and slows α -synuclein degradation, contributing to neurodegeneration in PD (Orenstein et al. 2013; Yue and Yang 2013).

Other genes that are more clearly linked to autophagy pathways have been associated with PD.

Mutations in ATP13A2 (PARK9) cause Kufor-Rakeb syndrome, which is an autosomal recessive form of early-onset parkinsonism with pyramidal degeneration and dementia (Ramirez et al. 2006). ATP13A2 is a lysosomal ATPase (Schultheis et al. 2004), which is highly expressed in the brain, and in particular in the substantia nigra. In idiopathic PD, its expression is up-regulated in surviving dopaminergic neurons, suggesting a role in protective mechanisms (Ramirez et al. 2006). Its mutation causes lysosomal dysfunction (Dehay et al. 2012; Usenovic et al. 2012) and results in parkinsonism and a lysosomal storage disorder (Bras et al. 2012). In case of LRRK2 mutations and consequent lysosomal dysfunction, ATP13A2 is up-regulated, showing a potential “rescue” system activated by the cell (Henry et al. 2015). ATP13A2 shows a close relationship with α -synuclein metabolism: it regulates its exosomal-secretion, accumulation, aggregation and has been demonstrated to be protective in case of α -synuclein overexpression (Usenovic et al. 2012; Kong et al. 2014; Tsunemi et al. 2014; Lopes da Fonseca et al. 2016).

ATP13A2 is linked with other PD pathogenic mechanisms: patients with mutations in ATP13A2 show mitochondrial dysfunction (Grünewald et al. 2012; Park et al. 2014), while its over-expression reduces oxidative stress in rotenone-induced mitochondrial damage (Holemans et al. 2015).

Other autophagy-related genes have been linked to PD (Fig.2) (Gan-Or, Dion, et al. 2015): mutations of VPS35, which encodes for a subunit of the retromer complex, have been linked to familial forms of PD with autosomal inheritance and low penetrance (Vilariño-Güell et al. 2011: 35; Zimprich et al. 2011: 35); the same gene has also been linked to Alzheimer disease (Small et al. 2005; Wen et al. 2011). The retromer complex recycles trans-membrane receptors from the endosome via the trans-Golgi network (Pfeffer 2001), and it is implicated in the homeostasis between protein degradation and accumulation. In PD dopaminergic neurons with mutations of VPS35 both a poor retrieval of LAMP2A and accumulation of α -synuclein have been demonstrated (Tang et al. 2015).

The most important discovery in PD research linking aetiology and pathogenesis to lysosomal function is the recognition that mutations of the gene for glucocerebrosidase represent the most important risk factor identified to date for the development of PD. This relationship will be the main focus of the present review.

MITOCHONDRIA DYSFUNCTION

A direct link between mitochondrial dysfunction and PD came with the discovery of a specific reduction of mitochondrial complex I activity in PD SN (Schapira et al. 1989). Subsequent to this discovery, mutations of genes linked to mitochondrial function and homeostasis were identified in familial forms of PD. Given their fundamental role and the potential for cell damage as a result of mitochondrial dysfunction, “mitochondrial quality” is governed by multiple control pathways, and parts of mitochondria are constantly replaced even under physiological circumstances. The main mechanism for the clearance of damaged mitochondria is mitophagy, a specific form of autophagy (Fig.3). Mutations of PINK1 and parkin are causes of autosomal recessive PD (Valente et al. 2004) and these proteins play important roles in mitochondria quality control. When a mitochondrion is damaged, its membrane is depolarized; at this point PINK1, a serine/threonine kinase, accumulates on the outer membrane to “mark it for degradation” and activate the mitophagy pathway through the recruitment of Parkin, which is an E3 ubiquitin ligase. This catalyses the polyubiquitination and initiates the degradation through the autophagosome-lysosome pathway; other proteins that interact with mitochondria (eg Mitofusin and Miro) are also involved in this process (Ashrafi and Schwarz 2013).

FBXO7 mutations cause parkinsonian-pyramidal disease (PPD), an early-onset form of parkinsonism (Di Fonzo et al. 2009). This gene (PARK15) encodes for an E3 ubiquitin ligase, which play important roles in

targeting proteins for ubiquitination and subsequent degradation (Deng et al. 2013) and participates in mitophagy.

Mutations of DJ-1 cause a familial early-onset form of PD (Bonifati et al. 2003): DJ-1 plays a crucial role in regulating calcium flux in the mitochondrion (Ottolini et al. 2013) protecting the cell by oxidative stress produced by the pace-making activity of dopaminergic neurons (Guzman et al. 2010: 1) and dopamine toxicity (Lev et al. 2009) and its deficiency causes an increased sensitivity to oxidative stress (Kim et al. 2005: 1).

There is a strong relationship between mitochondrial impairment and α -synuclein accumulation, which accumulation is associated with altered morphology and function of mitochondria and an increase in oxidative stress in a vicious circle, since oxidative stress increases the accumulation of α -synuclein. Increased activity of the PINK1/parkin pathway is neuro-protective in models of α -synuclein overexpression (Schapira and Gegg 2011).

GBA: activity and regulation

Glucocerebrosidase (GCase; glucosylceramidase; EC 3.2.1.45) is a lysosomal enzyme that metabolises glucosylceramide (GlcCer) to glucose and ceramide. GCase is encoded by the GBA gene, which is located on chromosome 1q21, comprises 11 exons and encodes a 497 amino acid protein of approximately 62 kDa which can be divided into three domains: Domain 1 (an antiparallel B-sheet), Domain 2 (containing the active site of the protein, a triose phosphate isomerase barrel) and Domain 3 (an 8-stranded B-barrel); there is an homologue pseudogene on the same chromosome. GBA transcription is modulated by the transcription factor EB (TFEB), which regulates the expression of a network of genes implicated in lysosome-mediated degradative pathways, named CLEAR (Coordinated Lysosomal Expression and

Regulation). TFEB colocalizes with mTORcomplex1 on the lysosomal membrane, and is important for the regulation of lysosomal biogenesis and activity, for lipid metabolism, autophagy and Ca⁺⁺ homeostasis in the lysosome. After its translation, GCase is translocated into the ER for post-translational modifications. GCase then binds to LIMP2 in the ER, is transported through the trans-Golgi network and finally localises in the membrane of the lysosome after a pH-dependent dissociation from LIMP2; in LIMP2 knock-out mice there is a reduction in GCase activity and an accumulation of the inactive enzyme. Under pathological circumstances, GCase co-localizes in the lysosome with a co-chaperone named Progranulin (PGRN), which is implicated in numerous cellular pathways, from inflammation and wound healing to aging. Glucocerebrosidase is activated by Saposin-C in the lysosome, but the mechanism by which this enzyme promotes lysosomal GCase hydrolysis is still undefined (Smith et al. 2017 Sep 18).

GBA AND PD

Defects in glucocerebrosidase cause autosomal recessive Gaucher disease (GD), which is the most common lysosomal storage disease worldwide, and has a particularly high prevalence among Ashkenazi Jews. Pathogenesis of GD is complex and includes deficits in macrophage function, cytokine and chemokine production and an imbalance between pro- and anti-inflammatory signalling and impaired regulation of inflammatory and reparatory cascades (Grabowski 2012).

It has been shown that obligate or confirmed carriers of GBA mutations had a higher risk of developing parkinsonism (Goker-Alpan et al. 2004). Definitive confirmation of the association between PD and GBA came from a large multicentre study, conducted on 5691 patients and 4898 controls, which found that GBA mutations were significantly prevalent among a heterogeneous population of PD patients with an odds ratio of 5.43 (Sidransky et al. 2009). Even if the proportion of PD patients with GBA mutations varies

depending on the population studied (more common in Ashkenazi) and sequencing method, between 5 and 25% of PD patients carry GBA mutations making this the most important genetic risk factor for PD discovered to date (Neumann et al. 2009; Schapira 2015). Heterozygous mutations of GBA confer a 10-30% chance of developing PD by age 80: a 20-fold increase compared to non-carriers; GD patients and asymptomatic heterozygous gene mutation carriers are at almost equal risk for development of PD (R N Alcalay et al. 2012; Anheim et al. 2012; Higuero et al. 2013; Rana et al. 2013). A study conducted on data from on a web-based assessment of PD prodromal markers to estimate the risk of PD showed that in the “high risk of PD group” the odds ratio of having GBA variant was 9.5 times greater than in other groups (Noyce et al. 2015). These observations were followed by the hypothesis that GBA mutations could increase the risk of other synucleinopathies: this was demonstrated in Lewy Body Dementia (Goker-Alpan et al. 2006; Nalls et al. 2013), while discordant evidence is available on multi-system atrophy (Segarane et al. 2009; Jamrozik et al. 2010; Mitsui et al. 2015).

GBA-PD CLINICAL FEATURES

GBA mutation carriers have slightly earlier onset (Sidransky et al. 2009; Gan-Or et al. 2010; Lesage et al. 2011; Zhang et al. 2015); there may be some association with the specific mutation in GBA (Lesage et al. 2011; Gan-Or, Amshalom, et al. 2015), e.g. those with the L444P mutation have a more aggressive course (Winder-Rhodes et al. 2013; Brockmann et al. 2014). There is contrasting evidence on the occurrence of L-dopa induced dyskinesias, since one study reported that levodopa induced dyskinesias were more severe in PD with GBA mutations than in controls (Lesage et al. 2011), but no difference was observed in another recent study (Zhang et al. 2015). The risk for dyskinesia in the GBA group most likely relates to the age of onset, as in young-onset PD. Non-motor symptoms have been found in PD patients who carry a GBA mutation: enteric, sexual and urinary dysfunctions, orthostatic hypotension, fatigue, pain, RBD and

others seem to be more common in this population (Brockmann et al. 2011; McNeill, Duran, Hughes, et al. 2012; Gan-Or, Mirelman, et al. 2015; Kresojević et al. 2015; Cilia et al. 2016 Sep).

Compared to idiopathic PD, GBA-PD patients show a higher risk for cognitive impairment (Zhang et al. 2015) and the cognitive decline seems to develop sooner (Winder-Rhodes et al. 2013; Brockmann et al. 2014; Oeda et al. 2015; Liu et al. 2016) and to affect different cognitive domains: memory and visuospatial domains (R. N. Alcalay et al. 2012), abstraction and orientation (McNeill, Duran, Hughes, et al. 2012), working memory, executive and visuospatial abilities (I.F. Mata et al. 2015) and visual short-term memory (Zokaei et al. 2014). PD patients with GBA mutations seem to be particularly susceptible to psychiatric symptoms: they show more frequent and earlier development of psychosis (Oeda et al. 2015; Cilia et al. 2016 Sep) and hallucinations (Li et al. 2014) (Barrett et al. 2014). Depression, anxiety and apathy have been reported to be more common in PD patients with GBA mutations (Brockmann et al. 2011; McNeill, Duran, Hughes, et al. 2012; Cilia et al. 2016 Sep), although this has not been confirmed in all studies (Nichols et al. 2009; R. N. Alcalay et al. 2012; Wang et al. 2013; Brockmann et al. 2014; Oeda et al. 2015).

Is there a genotype-phenotype correlation in GBA-PD?

Different GBA mutations have been suggested to result in different risks of developing PD: the odds ratios for PD ranged between 2.84 and 4.94 for mild mutation carriers and 9.92 and 21.29 for severe *GBA* mutation carriers (Gan-Or, Amshalom, et al. 2015). A study demonstrated that the most prevalent PD-associated GBA mutation is E326K, which interestingly has not been described in GD (Duran et al. 2013). Some clinical features associated with specific GBA mutations have been identified: E236K has been associated with rapid motor progression, postural and gait instability but not tremor, wearing off or dyskinesia (Oeda et al. 2015; Davis et al. 2016 Aug 29), and with a higher risk or a more aggressive

evolution of cognitive deterioration even though in the same domains as other PD patients (Winder-Rhodes et al. 2013; I.F. Mata et al. 2015; Davis et al. 2016 Aug 29). GBA mutations linked to neuropathic GD (such as L444P, 84GG, G195E, H255Q, R257Q, P266L, R359X, G377S, D409H, L444R, A456P, N462K, R120W and R463C) and complex alleles (E326K plus D140H mutations, E326K plus T369M, E326K plus R463C, E326K plus R257Q; and homozygotes carriers with E326K/E326K, T369M/T369M, and E326/E326K/L444P/L444P) but not those of non-neuropathic GD (N370S) have been associated with a more rapid cognitive decline (Liu et al. 2016). The risk of dementia in carriers of “severe” mutations (p.L444P, p.G377S, splicing mutation IVS10+1G>T) has been estimated to be 5.6 times higher than in idiopathic PD and 2.9 times higher than “mild” GBA mutations (p.N370S) (Cilia et al. 2016 Sep). No differences between mild and severe GBA mutations were found for the development of hallucinations (Barrett et al. 2014).

Studies have demonstrated that some prodromal signs of PD (impairment of olfaction, cognition, and subtle motor signs) (McNeill, Duran, Proukakis, et al. 2012) and thinning of the retinal ganglion cell layer (McNeill, Roberti, et al. 2013) were more frequent in asymptomatic GBA mutation carriers at baseline. A longitudinal study of the asymptomatic carriers of GBA mutations showed significant worsening of depression and motor signs and significant differences in smell, autonomic dysfunction, cognition and motor signs in comparison with controls (Beavan et al. 2015).

Non-Clinical Biomarkers

Imaging does not differentiate GBA-PD from other forms of PD: fluorodopa PET or single-photon emission computerized tomography (SPECT) with dopamine-sensitive ligands in PD-GBA patients shows asymmetric tracer loss in the posterior putamen, as seen in iPD (Goker-Alpan et al. 2012; McNeill, Wu, et

al. 2013) (Fig.4). In another study, both transcranial sonography (TCS) and positron emission tomography in GBA-PD did not show any difference when compared to iPD or LRRK2- PD, however this study was conducted on a small sample (Barrett et al. 2013); the findings on TCS were confirmed in another study (Kresojević et al. 2013). Discriminant features were identified in other brain regions using different techniques: a reduction of parietal and precuneus blood flow has been observed in GBA-PD. This finding is consistent with current knowledge on GBA: this pattern of cerebral blood flow is seen in Lewy body dementia (Goker-Alpan et al. 2012; Oeda et al. 2015).

White matter abnormalities involving the interhemispheric, frontal corticocortical, and parahippocampal tracts have been found in GBA-PD when compared to other PD patients (Agosta et al. 2013). A fMRI study found a significant decrease in cerebral metabolic rates of glucose in the supplemental motor area in patients with a GBA mutation, with additional hypometabolism in the parieto-occipital cortices in those who had parkinsonian signs (Kono et al. 2010). A reduced 123I-metaiodobenzylguanidine (MIBG) uptake in GBA-PD was demonstrated in early stages of the disease (Li et al. 2014), together with a reduction in the heart to mediastinum ratio, the degree of which correlated with the stage of PD and dementia (Li et al. 2014); however, this has not been confirmed by all studies (Oeda et al. 2015).

Different methods of studying GCCase activity in PD have been attempted: a reduction of GCCase activity has been demonstrated in the CSF of PD patients with and without GBA mutations (Parnetti et al. 2014; Parnetti et al. 2017 Aug 26) and LBD patients (Parnetti et al. 2009), although not consistently (van Dijk et al. 2013). The authors also found that a combination of β -glucocerebrosidase activity, oligomeric/total α -synuclein ratio, and age can discriminate PD from neurological controls with a sensitivity of 82% and a specificity of 71% (Parnetti et al. 2014). However, comparison between different studies must be carried

out with caution, given the high number of factors that influence lysosomal enzymes levels measurement in CSF (Persichetti et al. 2014). A reduction of GCCase activity has also been demonstrated in blood samples from patients with GBA mutations and non-GBA-PD (Alcalay et al. 2015).

Another way to assess GCCase activity is to measure intermediates and products of its metabolic pathways (Fig.5): GBA-PD patients show lower levels of fatty acids (omega-3 and omega-6) in the CSF (Schmid et al. 2012), measurement of fatty acids in the plasma of iPD patients demonstrated higher levels of all lipid species in PD patients versus controls, and higher levels of ceramide and monohexosylceramide were found in those with cognitive impairment (Mielke et al. 2013).

PATHOPHYSIOLOGY OF GBA in non-GBA mutation PD

There is evidence that GCCase activity might play a role in the pathogenesis of PD, even in those patients without GBA-mutations. A significant reduction in substantia nigra and striatum GCCase activity was identified in iPD brain and was related to the abnormal accumulation of α -synuclein, alterations in lysosomal and chaperone-mediated autophagy and lipid metabolism (Gegg et al. 2012) and was confirmed in a further study (Murphy et al. 2014). A decline in GCCase activity has also been seen in aging healthy controls (Rocha et al. 2015). A decreased GCCase activity was found in the substantia nigra and cerebellum of sporadic PD brains; there appears to be a relationship between α -synuclein and GCCase levels in brain (Schapira and Gegg 2013). α -synuclein accumulation occurs in case of: inhibition of GCCase with Condurotol B Epoxide (CBE) in SH-SY5Y cells and mice (Manning-Boğ et al. 2009; Cleeter et al. 2013), GBA KD in primary neurons, (Mazzulli et al. 2011), in iPSC from GBA-PD patients (Schöndorf et al. 2014), in the brain of mouse models of GCCase deficiency, in dopaminergic neurons generated from iPS from reprogrammed fibroblasts of a GD patient (Cullen et al. 2011; Mazzulli et al. 2011; Sardi et al. 2011; Osellame et al. 2013) and in a neural crest stem cell-derived dopaminergic neuronal model (Yang et al.

2017). Heterozygosity for GBA mutation worsens α -synuclein accumulation, as well as clinical manifestations, in a α -synuclein mutation mouse (Fishbein et al. 2014). For an extensive review of models of GBA-PD, see (Siebert et al. 2014; O'Regan et al. 2017 Jun 7).

It is proposed that, in neurons, deficient GCCase leads to accumulation of glucocerebroside which promotes aggregation of toxic α -synuclein oligomers through their stabilisation, and causes a decline in lysosomal proteolysis that selectively affects α -synuclein (Mazzulli et al. 2011). In fact, tau -which is another aggregation-prone protein involved in neurodegenerative diseases- does not accumulate; this finding is consistent with the selective role for GBA in synucleinopathies. Increase of α -synuclein has also been demonstrated in E326K mutation: an hypothesis is that this variant reduces GCCase activity enough to induce the accumulation of α -synuclein, but not of glucosylceramide (Duran et al. 2013).

Similar effects can occur in case of mutation of other genes that are important for GCCase function: LIMP-2 deficiency causes a reduction in GCCase activity and impaired autophagic/lysosomal function, lipid storage and α -synuclein accumulation with consequent neurodegeneration, inflammation and apoptosis, while its overexpression in cell lines reduces α -synuclein levels (Rothaug et al. 2014); TFEB downregulation results in a marked potentiation of α -synuclein toxicity and a modification of its subcellular localisation, with the reduction of its nuclear levels and subsequent inactivity, has been found in the midbrain of PD patients: it has been proposed that this could be secondary to the accumulation of α -synuclein, which sequesters TFEB in the cytosol (Decressac et al. 2013).

On the other hand, an increased level of α -synuclein may reduce GCCase activity through several different pathways: bio-physical studies revealed that, at a low pH, α -synuclein in its membrane-bound α -helical form selectively interacts with and inhibits GCCase (Yap et al. 2011; Yap et al. 2015) (Fig. 6). Moreover,

over-expression of α -synuclein leads to the downregulation of lysosome-resident glucocerebrosidase, inhibiting ER-to-Golgi and ER-to-lysosome trafficking (Cooper et al. 2006; Thayanidhi et al. 2010; Chung et al. 2013; Mazzulli et al. 2016).

Finally, it has been demonstrated that in mice with increased alpha-synuclein expression, the L444P GBA mutation enhances neuronal vulnerability to neurodegenerative processes (Migdalska-Richards, Wegrzynowicz, et al. 2017). On the contrary, in-vitro studies demonstrated that increasing the activity of glucocerebrosidase reduces α -synuclein accumulation: adeno-associated virus-mediated expression of exogenous GCase in GBA mutated (D409V/D409V) mice improved clinical and pathological features (Sardi et al. 2011; Yang et al. 2017); overexpression of glucocerebrosidase in the CNS of A53T α -synuclein mice reduced the levels of soluble α -synuclein (Sardi et al. 2013) and the use of ambroxol to increase GCase activity lowered α -synuclein levels in overexpression mice (Migdalska-Richards et al. 2016).

However, the relevance of GCase to PD is not limited to its interaction with α -synuclein. As already explained, in physiological conditions wild-type glucocerebrosidase is folded in the endoplasmic reticulum and translocated to the lysosomes. Misfolded GCase is arrested in the endoplasmic reticulum and undergoes polyubiquitination and degradation -causing ER stress- and triggers the UPR and ERAD (Ron and Horowitz 2005; Mu et al. 2008; Bendikov-Bar et al. 2011). Evidence for these processes was confirmed in studies conducted on iPSC derived from GBA-mutations carriers (Fernandes et al. 2016) and increased ERAD markers were found in GBA-PD brains (Gegg et al. 2012). A study suggested that parkin could play a determinant role in GCase degradation (Ron et al. 2010), however a further study performed on fibroblasts carrying biallelic parkin mutations demonstrated that parkin is not a fundamental E3-ubiquitin ligase for glucocerebrosidase (McNeill, Healy, et al. 2013).

A growing body of evidence suggests that GCase could interfere with mitochondrial function, another key mechanism in PD pathogenesis. Impairment in mitochondria function and morphology together with a reduced production of ATP and an increase in oxidative stress has been demonstrated in GCase inhibition (Cleeter et al. 2013), in fibroblasts from GD patients and in mice models of GD (Xu et al. 2014; M. de la Mata et al. 2015). For a review of mechanism of mitochondrial dysfunction in GCase deficiency, see (Gegg and Schapira 2016).

THERAPEUTIC IMPLICATIONS

Given the reciprocal relationship between glucocerebrosidase deficiency and α -synuclein deposition—several strategies are under investigation to enhance GCase function in order to slow, stop or reverse PD's neurodegenerative processes. There are two approved therapies for patients with GD: enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), the effects of which are—respectively—to enhance glucocerebroside degradation or to inhibit its production. ERT (mannose-terminal human glucocerebrosidase) is currently accepted as the first line therapy for GD and offers good results in GD type 1 patients (Shemesh et al. 2015) but is ineffective in neurological symptoms, since the enzyme does not pass the BBB (Schueler et al. 2002); at the moment, a peptide-linked recombinant glucocerebrosidase that targets neurons is in development (Gramlich et al. 2016). SRT (Cox et al. 2000) is used as a second line treatment because of the more common side effects (Shemesh et al. 2015). SRT crosses the BBB and therefore has been tested in GD type 3 in a randomized, controlled trial: however, it did not show significant benefits for the neurological features (Schiffmann et al. 2008).

Another strategy to treat GD is the use of small molecule chaperones, whose function is to facilitate correct folding and translocation of GCase, increasing its lysosomal levels and activity and preventing glycolipid accumulation. The most studied among these compounds is ambroxol (ABX); this drug was initially used to treat airway mucus hypersecretion and hyaline membrane disease in infants, and was then recognised as a pH-dependent, mixed-type inhibitor of GCase (Maegawa et al. 2009). ABX acts as a chaperone for GCase and enhances lysosomal function and autophagy through the activation of the CLEAR network via TFEB, LIMP2 and Sap-C upregulation (McNeill et al. 2014; Ambrosi et al. 2015). Importantly, ABX also shows antioxidant properties (Stetinová et al. 2004), is administrable orally and crosses the BBB (Luan et al. 2013). ABX improves trafficking of GCase to the lysosome and increases GCase activity in GD fibroblasts (Maegawa et al. 2009; Bendikov-Bar et al. 2011), and a recent pilot study in GD type 1 patients high-dose oral ambroxol was safe and well tolerated and improved some neurological features (Narita et al. 2016).

ABX has been tested in fibroblasts from GBA-PD, GBA mutations healthy carriers and in controls: it increased GCase activity and lysosomal function, and reduced α -synuclein accumulation in a neuronal cell line (McNeill et al. 2014). ABX treatment decreased α -synuclein levels and improved autophagy also in neural crest stem cell-derived dopaminergic neurons (Yang et al. 2017). Experiments in GBA mutant *Drosophila* demonstrated that ABX and isofagomine (see next section) improve GCase function, decreased ER stress and reversed the motor phenotype (Sanchez-Martinez et al. 2016). In wild-type mice, transgenic mice expressing the heterozygous GBA L444P and transgenic mice overexpressing human α -synuclein, ambroxol provided an increase in GCase activity and a decrease in both α -synuclein and phosphorylated α -synuclein protein levels (in the mice overexpressing human α -synuclein) (Migdalska-Richards et al. 2016). In healthy non-human primates the daily, oral administration of ABX resulted in a 20% increase in GCase activity in the midbrain, cortex, and striatum –similar to the mouse model

(Migdalska-Richards, Ko, et al. 2017). There are two clinical trials of amroxol currently underway in PD and PD dementia.

Other small-molecule non-inhibitory chaperones of glucocerebrosidase are under evaluation.

The iminosugar isofagomine (IFG) is an active-site inhibitor that facilitates the folding and transport of newly synthesized GlcCerase and has been shown to increase GCCase activity and reduce substrate accumulation in cell and mouse models (Steet et al. 2006; Khanna et al. 2010; Sun et al. 2012) of GD; although it was not successful in reducing the accumulation of lipid substrates in a model of neuropathic GD (Sun et al. 2011). Its efficacy was tested in a fly model of GBA-PD (Sanchez-Martinez et al. 2016). Oral administration of isofagomine in mice that overexpress human wild-type α -synuclein improved motor and olfactory performance, reduced microglial activation and reduced α -synuclein immunoreactivity in nigral DA neurons (Richter et al. 2014). NCGC607, which was tested in iPSCs differentiated into dopaminergic neurons -from patients with GD1, GD with parkinsonism and GD2- enhanced GCCase function, reduced glycolipids storage and the accumulation of α -synuclein (Aflaki et al. 2016)

Finally, given that autophagy is a fundamental process in PD and the pathogenesis of other neurodegenerative diseases, the possibility of enhancing this process using targets and pathways other than GCCase has been extensively studied: the most studied compound for this aim is rapamycin, which regulates autophagy through a mTor dependent network. Rapamycin has been shown to reduce α -synuclein accumulation and the consequent neurodegeneration in both cellular and animal models of PD. The application of autophagy-modulating agents in PD is further discussed in a recent review by (Moors et al. 2017).

CONCLUSION

Mutations of GBA are the most common genetic association with PD discovered to date and approximately 10% of PD patients carry such mutations. At present, they constitute a risk factor as only a minority of those that carry the mutations develop PD or a synucleinopathy. Evidence from a variety of in vitro and in vivo models indicate that GCase activity and α -synuclein levels have a reciprocal relationship, although the molecular mechanisms underlying this are not fully understood. Nevertheless, the therapeutic potential to manipulate this connection to enhance GCase and so reduce α -synuclein has been recognised and clinical trials are already underway evaluating the actions of amroxol in PD patients with and without GBA mutations, and in PD dementia, and the use of SRT in PD. These trials represent translational studies targeting the GCase pathway that offer the potential to modify the natural course of PD.

Table 1

Motor Symptoms	Non-Motor Symptoms
Tremor	Hyposmia
Rigidity	Psychiatric Symptoms: Depression, Anxiety, Apathy Hallucinations, Psychosis
Bradykinesia/Akinesia/Hypokinesia	Dementia/Cognitive Impairment
Postural Instability	Sensory Symptoms
Postural Abnormalities (Camptocormia, Pisa Syndrome)	Genito-Urinary Symptoms: Urinary Frequency, Urgency, Reduced Libido, Sexual Dysfunction
Gait Disturbances (Freezing of Gait, Festination, Start/Target/Obstacle Hesitation)	Gastrointestinal Symptoms: Constipation, Delayed/Reduced Stomach Emptying
Alterations in Blinking/ Eye Movements	Dysphagia, Sialorrhoea, Dysarthria, Hypophonia
Hypomimia	Disturbances of Sleep and Wakefulness
Micrographia	Cardiovascular Symptoms: Blood Pressure Variations (Postural, Post-Prandial), Dysrhythmias

Table 1. Motor and non-motor symptoms of Parkinson disease

(Schapira et al. 2017)

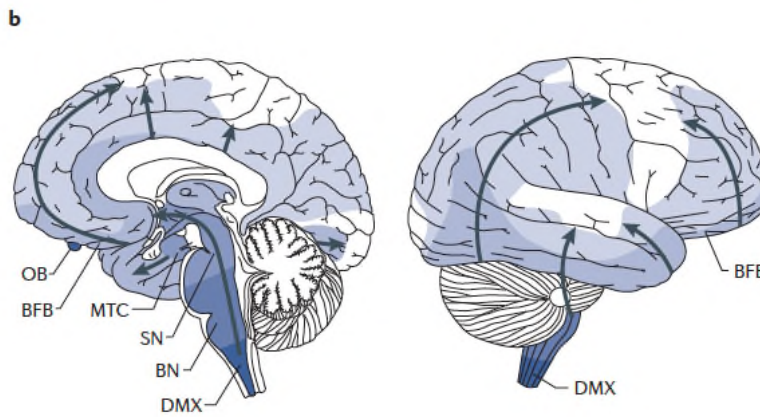
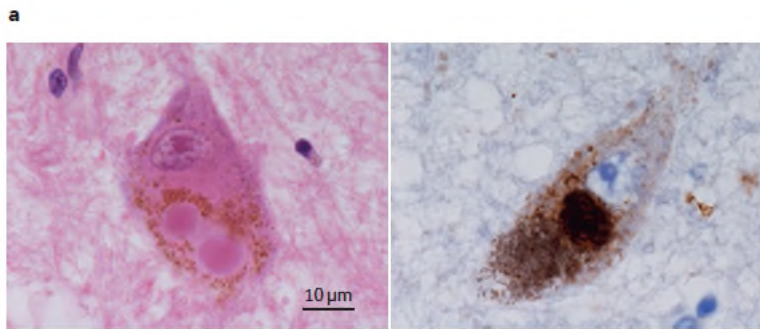


Figure 1a. Lewy bodies in Parkinson disease.

Right: haematoxylin-eosin staining; left: α -synuclein immunohistochemistry

Figure 1b. Hypothesized pattern of LB and α -synuclein deposition: starting in the dorsal motor nucleus of the glossopharyngeal and vagal nerves and anterior olfactory nucleus and progressively spread to the brain stem. In later stages, the involvement spreads firstly to the mesocortex and allocortex and finally to the neocortex (Fig.1b) (Braak et al. 2003) .

(Schapira et al. 2017)

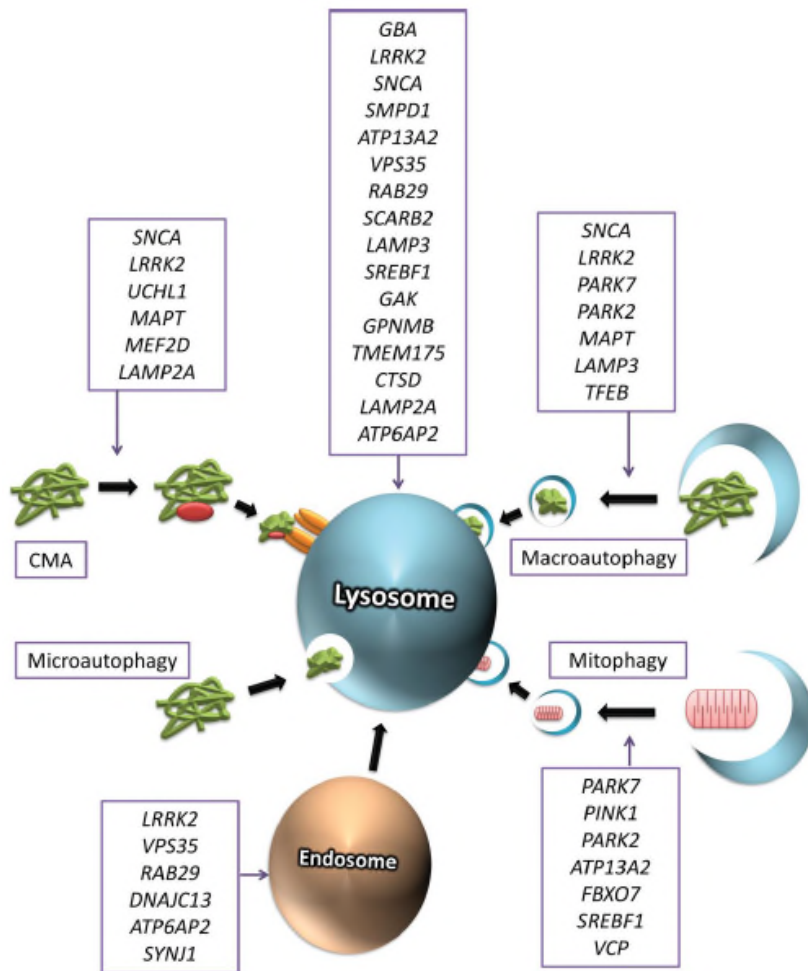


Fig.2 Genes involved in autophagy-lysosomal pathways which have been linked to PD
 (Gan-Or, Dion, et al. 2015)

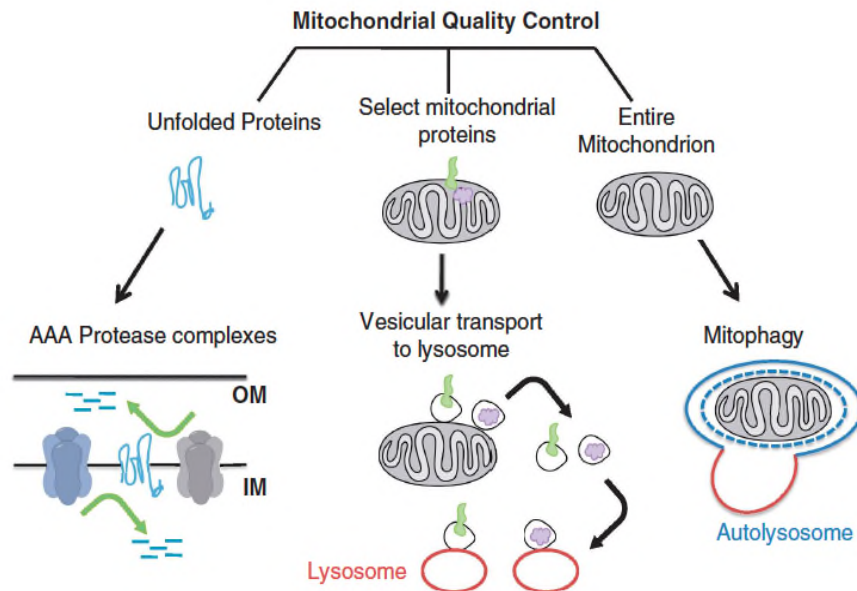


Fig.3 Major pathways of mitochondrial quality control.

Misfolded mitochondrial proteins can be degraded by AAA protease complexes (left) or by lysosomes, through vesicular transport (middle). Entire mitochondria can be degraded by mitophagy (right). (Ashrafi and Schwarz 2013)

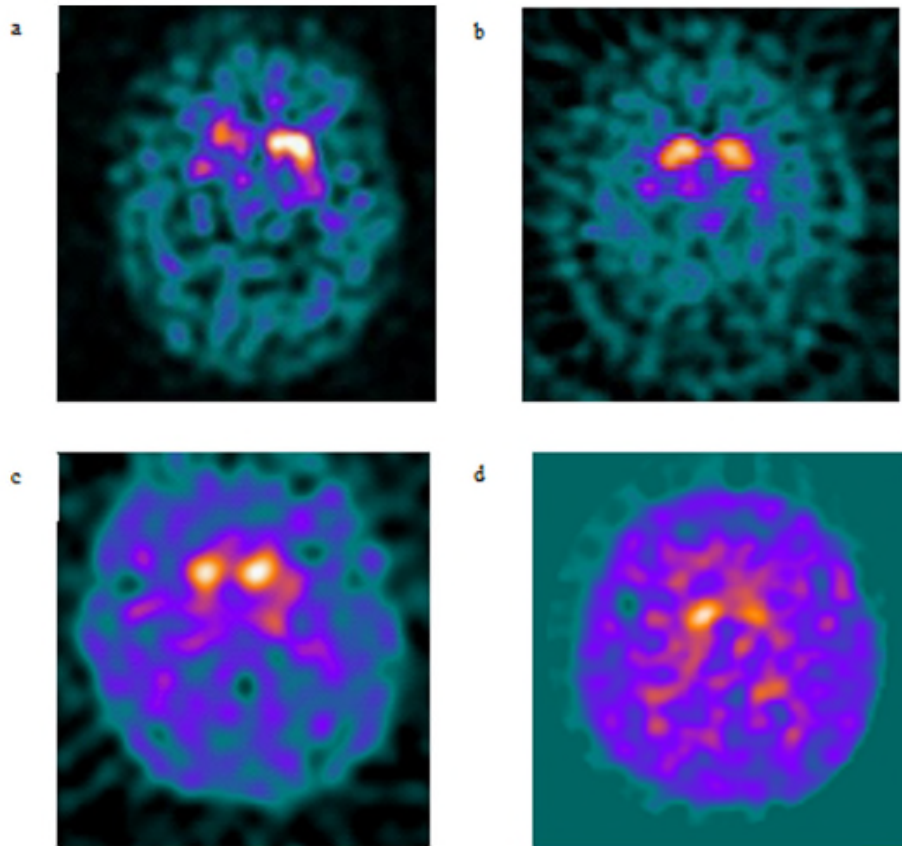


Fig.4 DaT SCAN in genetic PD and GBA mutations

- a) DaT SCAN from a 50 years old man with GBA mutation
 - b) DaT SCAN from a 67 years old woman with PINK1-associated PD
 - c) DaT SCAN from a 45 years old man with Parkin-associated PD
 - d) DaT SCAN from a 32 years old woman with LRKK2 mutation
- (McNeill, Wu, et al. 2013)

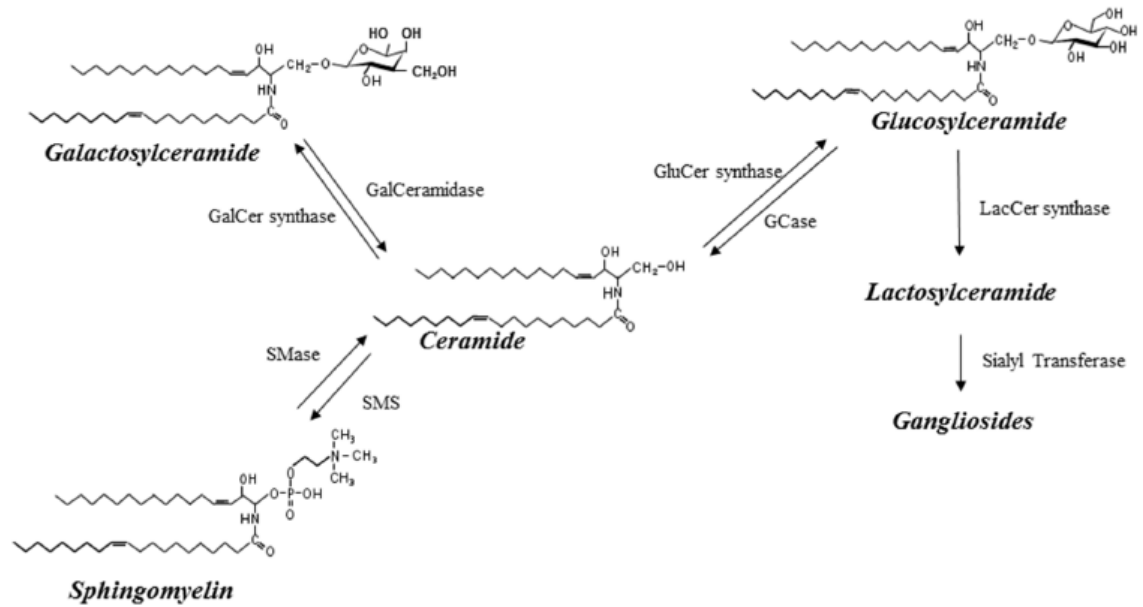


Fig.5 Ceramide and glycolipid metabolism.

(Mielke et al. 2013)

Abbreviations for enzymes are as follows: GCase: glucocerebrosidase; GalCer synthase: galactosylceramide synthase; GluCer synthase: glucosylceramide synthase; GalCeramidase: galactosylceramidase; LacCer synthase: Lactosylceramide synthase; SMase: Sphingomyelinase; SMS: Sphingomyelin synthase.

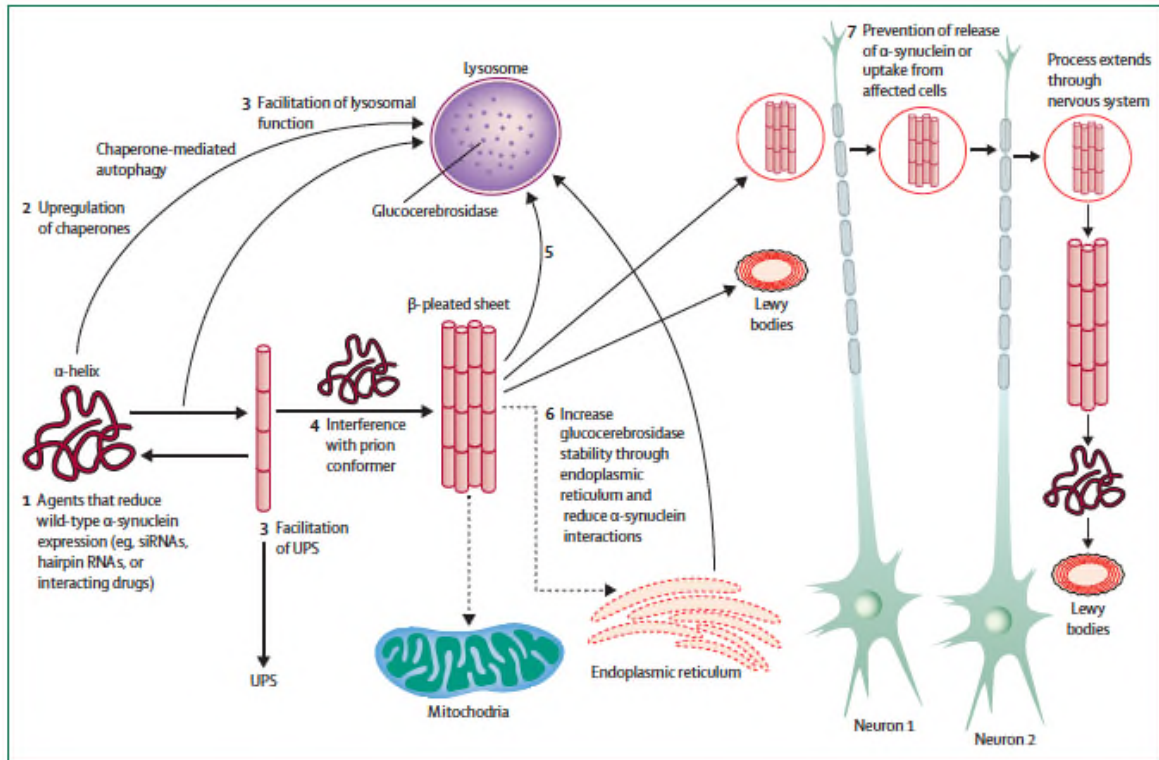


Fig.6 Pathways for potential interventions in the treatment of aberrant α -Synuclein

(Schapira et al. 2014)

(1) agents that reduce expression of wild-type α -synuclein and thus reduce the natural substrate for a prion or templating reaction; (2) upregulation of chaperones that promote refolding or clearance of abnormal proteins; (3) facilitation of UPS or autophagy/lysosomal function to promote clearance of unwanted proteins; (4) interference with the prion conformer whereby misfolded α -synuclein acts as a template to promote the conversion of wild-type α -synuclein; (5) agents or immune approaches targeted to remove toxic α -synuclein oligomers or aggregates; (6) increased glucocerebrosidase stability or trafficking through the endoplasmic reticulum to normalise α -synuclein metabolism and lysosomal function. These interventions (1–6) are designed to prevent or reduce the toxic effects of α -synuclein oligomers or aggregates on vital cell processes (eg, mitochondrial function and axonal transport). intervention (7) represents agents that prevent release of α -synuclein from affected cells and/or the uptake of α -synuclein into healthy unaffected cells whereby the process might extend throughout the nervous system. 6 Dashed arrows represent inhibition and solid arrows represent pathways of progression. UPS=ubiquitin proteasome system.

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