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NEUROLOGICAL UPDATE

Glucocerebrosidase and parkinsonism: lessons to learn

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Abstract Both homo- (causing autosomal-recessive Gaucher's disease; GD) and heterozygous mutations in the *glucocerebrosidase* gene (*GBA*) are associated with Parkinson's disease (PD), and represent the most robust known genetic susceptibility factors identified in PD. Since the accumulation of α-synuclein has been considered critical to the pathogenesis of PD among several possible pathways through which glucocerebrosidase (GCase) deficiency may promote the pathogenesis of PD, particular attention was given to the reciprocity with α-synuclein levels, lysosomal dysfunction, endoplasmatic reticulum–Golgi trafficking of GCase, dysregulation of calcium homeostasis and mitochondrial abnormalities. The proportion of PD patients that carry *GBA* mutations is estimated to be approximately between 5 and 10 %. Individual PD patients with or without *GBA* mutations cannot be discriminated on clinical or pathological grounds. However, *GBA* mutation carriers may have slightly earlier age at PD onset, more likely have a positive family history for PD, and more prevalent non-motor symptoms when compared to those patients who are not carriers. Establishing the concept of *GBA*-related PD promoted a search for the pathogenic mechanisms through which GCase deficiency may influence pathogenesis of PD, suggesting that targeting the GCase–lysosomal pathway might be a rational approach for the development of neuroprotective drugs in PD.

Keywords Parkinson's disease · Gaucher disease · Glucocerebrosidase · Lysosome · α-synuclein

Both homo- (causing autosomal-recessive Gaucher's disease; GD) and heterozygous mutations in the *glucocerebrosidase* gene (*GBA*) are associated with Parkinson's disease (PD), and represent the most robust known genetic susceptibility factor identified in PD [1, 2]. Neudorfer et al. [3] in 1996 reported six patients with GD type 1 who developed progressive parkinsonism refractory to conventional antiparkinsonian therapy, although GD patients with some features of parkinsonism were sporadically reported as early as 1939 [4]. In 2004 it has been shown that mutations in the *GBA* gene were more frequent in PD patients than in controls, and that heterozygous carriers of the *GBA* mutation might have an increased risk to develop PD [5, 6]. The main confirmation of such association was the extensive multicentric study (5691 PD patients and 4898 controls) that found the odds ratio of 5.43 for detecting any *GBA* mutation in PD patients compared to the controls [7].

Proposed mechanism for GBA-associated parkinsonism

Glucocerebrosidase (GCase) is a lysosomal enzyme that hydrolyzes β-glycosyl linkage of glucosylceramide (GlcCer) to glucose and ceramide [8, 9]. Different mechanisms have been proposed in attempt to elucidate common pathological links between *GBA* mutations and PD, including glia-mediated inflammatory response and α-

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synuclein accumulation. Astrocytosis and microglial activation were described both in human GD brain samples, as well as in Gba-deficient mouse model of neuronopathic GD [10–12]. The latter model demonstrated that glial cells' activation preceded neuronal loss in affected brain regions and that the level of inflammatory mediators correlated with disease progression [11]. Futhermore, recent reviews provided extensive analysis of the cellular relationship between GCase and α-synuclein (αS) [13–15], but the mechanisms underlying the relation between *GBA* mutations and the development of PD is still not clear. There is clinical, genetic and experimental evidence for both mutant *GBA*-mediated loss-of-function or toxic gain-of-function hypotheses, which are not mutually exclusive [1, 16].

The loss-of-function theories mainly focus on altered lipid metabolism and speculate that *GBA* mutations result in unstable or deficient protein, that, due to a lack of enzymatic activity, contributes to accumulation of GCase substrate, GluCer, within the lysosome, altering the cell membrane sphingolipid composition. Membrane binding is a key biological feature of αS and many functions of αS occur in association with lipid membranes. For example, in Lewy bodies (LB) αS layers are formed around central lipid core [17]. Hence, accumulation of GluCer can change lipid homeostasis, with subsequent alterations in αS processing. In support to this theory, null *GBA* alleles have been reported in PD patients and chemical inhibition of *GBA* could lead to accumulation of αS [18], a finding that was later replicated in different models with *GBA* mutations [16, 19–21]. Even in brains of PD patients without *GBA* mutations (PD-non-*GBA*), the reduction of GCase enzymatic activity was associated with increased αS levels [22].

The gain-of-function theories elaborate the effect of misfolded mutant GCase. Most *GBA* mutations are missense mutations, resulting in a misfolded protein. The presence of mutant GCase was confirmed in a significant proportion of αS inclusions in brain samples of GD and PD patients [1, 21]. The abnormal conformation can affect lysosomal function and cellular proteostasis systems and lead to αS accumulation, either due to increased formation of αS aggregates, or decreased clearance. Studies on fibroblasts derived from patients with GD showed that mutant GCase failed to fold correctly and was therefore retained in the endoplasmic reticulum (ER), overwhelming ubiquitin–proteasome system [23–25]. As a result, lysosomal GCase levels were significantly decreased, with subsequent accumulation of GluCer. Indeed, most mutant alleles identified in patients with *GBA*-associated PD (PD-*GBA*) were missense mutations that resulted in a misfolded protein. Moreover, mutant GCase was found in LB, suggesting its role in αS oligomerisation or impaired degradation [1].

Glucocerebrosidase, α-synuclein and lysosomes: a vicious circle

Deficient lysosomal GCase activity causes accumulation of GlcCer that in turn, accelerates formation and stabilizes soluble αS oligomers. Increased αS oligomers inhibit ER–Golgi trafficking of GCase and its translocation to the lysosome, resulting in further decrease in GCase lysosomal activity [20, 26, 27]. This amplifies GlcCer accumulation and stabilization of soluble αS oligomers, and results in a stronger inhibition of GCase ER–Golgi trafficking with each pathogenic cycle, resulting in more αS aggregates [20]. This way, bidirectional interaction between αS and GCase creates a positive feedback loop that, after a certain threshold, leads to self-propagating disease. Such *reciprocal interaction* between GCase and αS may underlie the aggregation of αS in the brain of PD-*GBA* patients. Data from autopsies of PD-*GBA* patients revealed elevated levels of oligomeric αS and αS-immunoreactive LB in the cortex and hippocampus [28]. However, some studies failed to demonstrate the effect of GCase pharmacological inhibition on αS accumulation/aggregation via lysosomal dysfunction [29].

In vitro experiments showed that in the lysosome-enriched fractions isolated from brain tissues and cultured neuronal cells, αS directly inhibited the lysosomal GCase activity (oligomers > monomers) [30]. It was shown that lysosomal GCase interacts with the C terminus of αS under acidic conditions, which mimicked the lysosomal lumen [31], and that membrane-bound α-helical form of αS inhibited GCase hydrolytic activity [32]. It is not known why αS oligomers inhibit GCase activity more strongly than the monomers. One possibility is that αS oligomers have a higher binding affinity with GCase and can therefore modulate its enzymatic activity to a greater extent. The colocalization of αS and GCase in LB indicates that aggregated αS can tightly bind to GCase [33]. In cultured neuronal cells, in addition to directly inhibiting GCase, αS oligomers may indirectly reduce GCase activity by blocking its transport from the ER to the lysosomes [20, 27].

GCase is located on the surface of the inner membrane of the lysosome. Under normal conditions, newly synthesized GCase is correctly folded in the ER and then translocated to the lysosomes by the trafficking receptor, lysosomal integral membrane protein-2 (LIMP-2) [34]. Cells overexpressing αS show less GCase delivered to the lysosome, as a result of less binding to LIMP-2 [35]. Since LIMP-2 is crucial for the correct trafficking of GCase and that its malfunction may lead to a reduction in GCase levels and activity, it is interesting to consider possible role of LIMP-2 in the development of PD. In LIMP-2 *knock-out* mice, lysosomal GCase activity was reduced, resulting in αS accumulation and disturbed lysosomal function, leading to neurotoxicity in dopaminergic neurons [36].

The main lysosomal degradation pathway for wild-type alpha αS is chaperone-mediated autophagy (CMA) [37]. Proteins destined for CMA form a complex with cytosolic chaperone, heat shock cognate protein of 70 kDa (Hsc70), which is targeted to the lysosomal membrane where it interacts with lysosomal associated membrane protein 2A (LAMP-2A), the receptor for CMA of αS, and undergoes translocation to the lysosome, followed by degradation [38]. To transport αS into the lysosome, the LAMP-2A protein must form a multimeric complex on the lysosomal membrane [39].

Namely, LAMP-2A exists as a monomer at the lysosomal membrane, in specific membrane lipid microdomains and substrate proteins only bind to monomeric LAMP-2A. To translocate substrate across the lysosomal membrane, it forms a multimeric complex with other proteins, enabling translocation of the substrates into the lysosomal lumen, which only relates to LAMP-2A molecules outside these microdomains [40]. Retention of LAMP-2A within the lipid microdomains may not allow protein-complex formation, which in turn will prevent the translocation of αS, resulting in its accumulation in the cytosol (Fig. 1).

In a cellular and mouse models of GD, *GBA* inhibition results in changes of lysosomal membrane composition, including increased concentration of GCase in lipid rafts [41, 42]. It was hypothesized that this process may prevent or reduce the formation of LAMP-2A protein-complexes, which will then reduce the removal of αS by CMA and increase its accumulation in cytosol [43]. In another study, LAMP-2A protein levels were found to be selectively decreased, which directly correlated with increased levels of αS and decreased levels of Hsc70 in the same PD samples, as well as with accumulation of cytosolic CMA substrate proteins, MEF2D and IkBα [44]. It is possible that alterations in the composition of the lysosomal membrane may affect autophagy-lysosomal pathways in general, hypothetically contributing to PD development.

The role of aging

Aging, an important risk factor for PD, is associated not only with decline in efficiency of the mechanisms responsible for disposal of misfolded proteins in post-mitotic neurons, but also with decline of GCase activity [45]. Age-related increase of oligomeric αS levels in the brains of cynomolgus monkeys was accompanied by a decrease in the expression and activity of GCase [30]. Besides, levels of αS phosphorylated at serine 129, a modification that promotes its oligomerization, also increase with age in the brain and are associated with a reduction in the activity of protein phosphatase 2A (PP2A), an enzyme that facilitates αS dephosphorylation [30]. In the light of described deleterious αS-GCase feedback loop, aging-related αS accumulation may affect GCase activity even in PD-non-GBA patients. Indeed, decreased GCase protein levels and enzymatic activity were recently identified in the substantia nigra (SN) of PD-non-GBA patients [22, 35, 46], that might, unlike general lysosomal inhibition, increase the levels of intracellular αS [18, 47]. Interestingly enough, reduced GCase occured when cellular αS levels were increasing, but before αS deposition in LB, and correlated with reduced LAMP-2A and increased αS levels [22].

Glucocerebrosidase affects α-synuclein cell-to-cell transfer

Although initially thought to be a purely intracellular protein, it gradually became clear that αS could be detected in the conditioned medium of cells and in extracellular fluids, such as plasma and CSF [48, 49]. Recent evidence has pointed towards the significance of cell-to-cell transfer of αS aggregates in PD and other synucleinopathies, as a mechanism of disease propagation [50, 51]. The existence of extracellular αS in rodent and human brain interstitial fluid has been confirmed by microdialysis [52]. Importantly, secreted αS can impact neuronal homeostasis and lead to neuronal death, even at concentrations close to those identified in body fluids [51, 53]. It is conceivable that GCase depletion may increase αS release, while the endolysosomal dysfunction increases its uptake [54, 55]. A recent report described increased neuronal cell-to-cell transmission of endogenous αS in grafted cells lacking GCase [47]. Furthermore, the ectopic expression of wild-type GCase (but not of an activity-deficient *GBA* mutant) reversed the effects of *GBA* deletion on the propagation of αS aggregates, indicating that the enzyme hydrolytic activity had a role in cell-to-cell αS transfer [47].

How frequent are *GBA* mutations among PD patients?

More than 300 different mutations of the *GBA* have been reported, but the N370S (the most frequent among European populations and Ashkenazi Jews) and L444P (dominated in Asian populations, where N370S was rare) account for the majority of those found in both GD and PD. Both GD patients and asymptomatic heterozygous gene carriers were recognized to be at risk of PD [15]. The proportion of PD patients that carry *GBA* mutations is estimated to be approximately between 5 and 10 % [7, 56–59] (range 3.2–21 %) [5, 6, 60]. The highest frequency of *GBA* mutations in PD patients (31.1 %) was reported in Ashkenazi Jews [5], while studies in Norwegian [61] and North African Arab-Berber [62] populations failed to demonstrate different frequencies among PD patients and controls (Table 1).

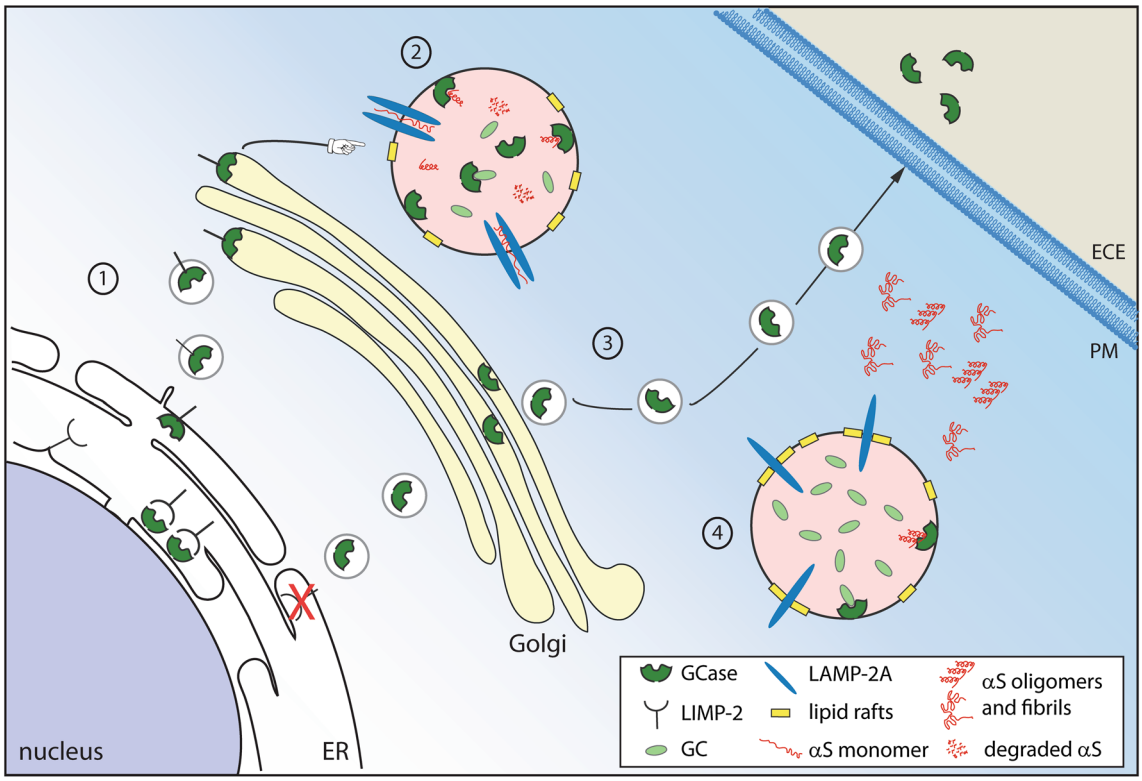

Fig. 1 Interaction between glucocerebrosidase, α synuclein, and lysosomes (adapted from Siebert et al. Ref. [13]). *1* After selective recognition by the lysosomal integral membrane protein-2 (LIMP-2), glucocerebrosidase (GCase) is sorted via ER and Golgi to the lysosomes. *2* Inside the lysosomes, GCase is associated with inner face of the lysosomal membrane, and hydrolyzes its substrate, glucocerebroside (GC), thus enabling the maintenance of the lysosomal membrane composition. In addition, α synuclein (αS) monomers interact with lysosomal associated membrane protein 2A (LAMP 2A), and upon formation of multimeric complex, enter the lysosome, where GCase facilitates their breakdown. *3* In case of LIMP-2 deficiency or absence, GCase is not sorted to the lysosomes, and is therefore secreted into the extracellular environment. *4* Impaired GCase activity may affect lysosomal membrane composition, leading to increased density of lipid rafts, affecting the formation LAMP 2A-protein-complexes required for αS translocation across lysosomal membrane, resulting in its accumulation in the cytosol. The increased cytosolic level of soluble monomers facilitates formation of oligomers and fibrils, affecting regular traffic of GCase from ER to Golgi. *LIMP-2* lysosomal integral membrane protein-2, *GCase* glucocerebrosidase, *ER* endoplasmic reticulum, *GC* glucocerebroside, *αS* α synuclein, *LAMP 2A* lysosomal associated membrane protein 2A, *PM* plasma membrane, *ECE* extracellular environment

GBA mutations are important risk factor for developing PD, but most people with mutations will never develop PD [63]. Patients with GD have an almost 20-fold increased life-time risk of developing PD [64], irrespective of either GD severity or enzyme replacement therapy [65]. Carriers of severe (for example L444P) when compared to those with mild *GBA* mutations (for example N370S) have three to four times higher risk to develop PD, characterized by an earlier age at onset (on average 5 years) and more common cognitive impairment [66, 67].

Risks for PD at the age of 60 and 80 years was 4.7 and 9.1 % for GD patients and 1.5 and 7.7 % for *GBA* mutations carriers, respectively [68]. Cumulative risk for PD for *GBA* mutations carriers was 5 % at the age of 60 rising to 15 % at the age of 80 years [58], while Rana et al. [69] reported risks of 2.2 and 10.9 % at the age of 65 and 85 years, respectively. Due to the high cumulative age-specific risk (i.e. penetrance) found in the study by Anhelm et al. [70] (29.7 % at the age of 80 years), it has been suggested that *GBA* might be considered as an autosomal-dominant PD causing gene with reduced penetrance, although, these results should be interpreted with caution.

It is not surprising that the first-degree relatives of GD patients more frequently have PD, since they are obligate heterozygous *GBA* carriers [71–73]. PD patients with affected relatives are more frequently carriers of *GBA* mutations than those with negative family history for PD [57].

Clinical characteristics of Parkinson's disease associated with *GBA* mutations

Pathological examinations of PD-*GBA* patients have revealed morphological abnormalities within the spectrum of classical (idiopathic) PD; therefore, this condition is not considered to represent an atypical form of the disease [33,

Table 1 Frequency of *GBA* mutations in patients with Parkinson's disease (updated table from Ref. [1]; only studies with more than 100 patients with Parkinson's disease and included controls were analyzed)

	Population	Screened mutations	Number of participants		Carrier frequency (%)		p value	Most common variants
			Cases	Controls	Cases	Controls		
Clark et al. [114]	Ashkenazi	N370S	160	92	10.7	4.3	0.20	N370S
Toft et al. [61]	Norwegian	N370S, L444P	311	474	2.3	1.7	0.58	N370S
Tan et al. [74]	Chinese	L444P, N370S	331	347	2.4	0.0	0.06	L444P
Wu et al. [75]	Chinese	L444P, Rec*Nci*I, R120W	518	339	3.1	1.2	0.07	L444P, Rec*Nci*I
Clark et al. [76]	Mixed (64 % Jewish)	GBA exons	278 (178)	179 (85)	13.7	4.5	–	N370S, c.84dupG
De Marco et al. [115]	Italian	N370S, L444P	395	483	2.8	0.2	0.0018	L444P
Mata et al. [116]	Mixed	N370S, L444P	721	554	2.9	0.4	0.001	N370S, L444P
Gan-Or et al. [89]	Ashkenazi	N370S, R496H, L444P, c.84dupG, IVS2+1, V394L, D409H, RecTL	420	333	17.9	4.2	<0.0001	N370S
Kalinderi et al. [117]	Greek	GBA exons	172	132	4.7	0.8	0.048	H255Q, L444P
Nichols et al. [77]	Mixed (<10 % Jewish)	N370S, T369M, L444P, IVS6, IVS10, E326K, K303K, R262H, Rec*Nci*I	1325	359	12.6	5.3	–	E326K, T369M, N370S, L444P
Neumann et al. [59]	British	GBA exons	790	257	4.2	1.2	0.01	L444P, N370S
Mitsui et al. [100]	Japanese	GBA exons	534	544	9.4	<0.1	<0.0001	R120W, Rec*Nci*I
Bras et al. [118]	Portugese	GBA exons	230	430	6.1	0.7	–	N370S, N396T
Mao et al. [88]	Chinese	L444P	616	411	3.2	0.2	0.001	–
Sun et al. [119]	Chinese	L444P, F213I, R353W, N370S	402	413	2.7	0.0	0.0007	L444P
Hu et al. [120]	Chinese	N370S	328	300	1.8	0.7	0.29	–
Lesage et al. [121]	North African (Algeria, Morocco, Tunisia, Libya)	GBA exons, LRRK2 (G2019S)	194	177	4.6	0.5	0.01	N370S, L444P, Rec*Nci*I
Moraitou et al. [122]	Greek	N370S, L444P, D409H, H255Q, R120W, Y108C, IVS10-1G>A, IVS6-2A>G	205	206	10.2	3.4	0.006	N370S
Noreau et al. [123]	French-Canadian	GBA exons	212	189	3.8	0.5	0.10	L444P, p.L236F, p.S378L, p.W417G
Lesage et al. [57]	European	GBA exons	1130	391	6.7	1.0	<0.0001	N370S
Huang et al. [93]	Chinese	GBA exons	967	780	3.7	0.3	0.0001	L444P
Setó-Salvia et al. [78]	Spanish	GBA exons	225	186	9.8	0.5	0.016	N370S, L444P
Emelyanov et al. [124]	Russian	N370S, L444P	330	240	2.7	0.4	0.038	N370S
de Carvalho Guimarães et al. [125]	Brazilian	N370S, L444P	237	186	3.4	0.0	–	–
Choi et al. [60]	Korean	GBA exons	277	291	3.2	0.0	0.01	N188S, P201H, R257Q, S271G, L444P

Table 1 continued

	Population	Screened mutations	Number of participants		Carrier frequency (%)		p value	Most common variants
			Cases	Controls	Cases	Controls		
Wang et al. [126]	Chinese	L444P, N370S, R120W	208	298	3.4	0.3	0.007	L444P
Zhang et al. [127]	Chinese	L444P, N370S, R120W	195	443	3.1	0.0	0.001	L444P
Kumar et al. [56]	Serbian	GBA exons 8–11	360	348	5.8	1.4	0.0041	N370S
González-Del Rincón et al. [128]	Mexican Mestizo	N370S, L444P	128	252	5.5	0.0	–	L444P
Yu et al. [129]	Chinese	GBA exons	184	130	8.7	1.54	0.0072	L444P
Li et al. [94]	Japanese (familial PD)	GBA exons	147	100	18.8	1	<0.0001	L444P
Pulkes et al. [90]	Thai	GBA exons	480	395	5.0	0.5	<0.001	–
Asselta et al. [130]	Italian	GBA exons 9-10	2350	1111	4.5	0.63	2.2×10^{-11}	N370S
Grimes et al. [131]	Canadian	GBA exons	225	110	4.4	0.91	0.088	N370S, L444P
Gan-Or et al. [67]	Ashkenazi-Jewish	N370S, R496H, 84GG, IVS2 + 1, V394L, D409H, L444P, RecTL	1000	3805	19.2	6.4	<0.0001	N370S

59]. Autopsy study also found that cortical LB are more frequently seen in PD-*GBA* patients than in non-carriers [59]. Clinically, *GBA* mutation carriers have an earlier age at PD onset (between 1.7 and 6.0 years earlier than PD-non-GBA [1, 5, 74–77]; observation not confirmed in several studies) [56, 78, 79], more likely have a positive family history for PD, but also more prevalent non-motor symptoms (NMS) when compared to PD-non-GBA [80].

Both GD patients and asymptomatic *GBA* mutation carriers may exhibit mild parkinsonian motor signs insufficient to reach the diagnosis of PD that may remain stable after two years of follow-up [81, 82]. In addition, hyposmia, cognitive decline, REM-sleep behavior disorder and depressive symptoms are more frequent among them in comparison to subjects who are not carriers of *GBA* mutations [81, 83]. We identified a family where both parents of a GD patient (obligate *GBA* carriers) have stable mild parkinsonian signs during the follow-up of 3 years (Fig. 2).

PD-*GBA* has typical clinical manifestations: asymmetric parkinsonism with a good response to levodopa [84]. PD phenotype in GD patients and heterozygous *GBA* mutations carriers is similar [1]. Rarely, PD may precede clinical manifestations of GD for years [56, 85]. Initial symptoms of PD seem to be similar between *GBA* mutations carriers and non-carriers [5, 86–88]. However, although not confirmed in all studies, there are reports of more common bradykinesia, tremor, weakness and shoulder pain, as well as a lower frequency of rigidity as initial symptoms in PD-*GBA* [76, 86, 89].

Motor phenotype

When diagnosed, PD-*GBA* is clinically indistinguishable from PD-*non-GBA* [57, 76, 77, 79, 88, 90, 91]. However, some studies suggested less prevalent asymmetric onset, more postural instability [7, 56, 87], and more frequent levodopa-induced motor fluctuations and dyskinesia (LID), in PD-*GBA* patients [57, 92] (conversely, other studies observed that LID occurred with a lower frequency or with a similar prevalence when compared to PD-non-GBA patients) [93–96]. In conclusion, individual PD-*GBA* patients cannot be discriminated from PD-non-*GBA* patients on clinical or pathological grounds.

GBA mutations and polymorphisms influence the course of PD [79]. Progression of motor deterioration is more rapid in PD-*GBA* than in PD-non-GBA patients: *GBA* mutations carriers have fourfold increased risk of progression to Hoehn and Yahr stage 3 (HY3) [79, 90, 97–99]. Winder-Rhodes et al. [79] estimated that the time of progression to HY3 was 23.5 months for PD-*GBA* patients, 32 months for PD patients with *GBA* polymorphisms, and 49 months for non-carriers.

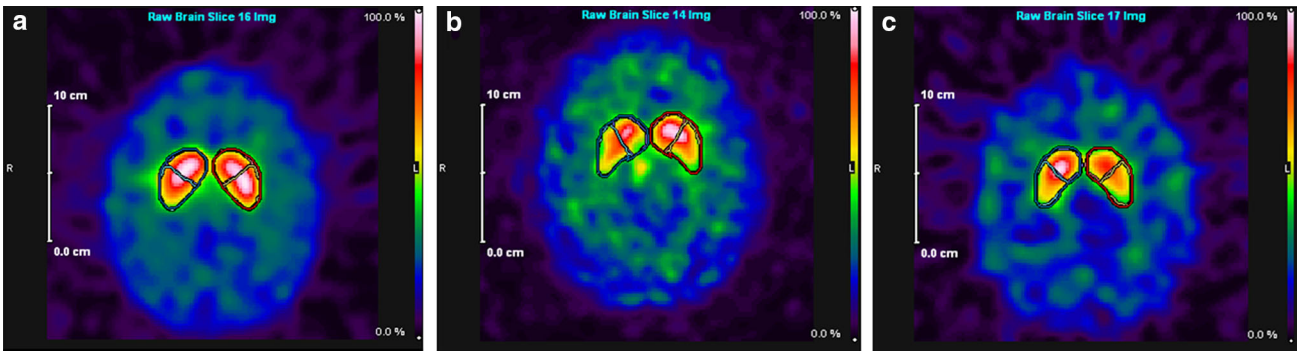

Fig. 2 DaT-SPECT findings in *GBA* mutation carriers in premotor phase of PD. **a** Normal DaT-SPECT in a person without parkinsonism and without *GBA* mutations; **b** and **c** show DaT-SPECT findings for parents of GD patient. GD patient doesn't have any signs of parkinsonism, hence, both parents (obligate carriers of *GBA* mutations) are in premotor phase of PD. **b** father of our GD patient (55 years) had no criteria for PD, but expressed hyposmia, REM-sleep behavior disorder, hypomimia, and mild bradykinesia of the *left leg*, that were stable for a 3 year follow-up and *bilateral*, but predominantly *right-side* decrease in DaT-SPECT binding; **c** mother of the same GD patient (51 years) had only bradykinesia of the right extremities that was stable for 3 year follow-up and reduced striatal DaT binding bilaterally, predominantly on the *left side*

Non-motor features

Prominent NMS appeared to be the key clinical aspect of PD-*GBA* patients: they suffered more commonly and severely from a variety of NMS than those without *GBA* mutations [58, 80, 87]. PD-*GBA* patients show more rapid progression of cognitive decline and have >5fold increased risk of progression to dementia when compared PD-non-*GBA* patients [78, 79, 96, 98]. Winder-Rhodes et al. calculated projected median time to dementia to be 46 months for PD-*GBA* patients, 96 months for PD patients with *GBA* polymorphisms, while <50 % of those without GBA mutations developed dementia over the median follow-up period of 82 months [79].

Visual hallucinations, delusions and psychosis occured in PD-*GBA*, probably due to an extension of the LB pathology to the temporal lobe [55, 94, 95]. Depression, apathy, indifference, and anxiety disorder have been, although not uniformly, [89, 98, 101–103] reported to have higher prevalence in PD-*GBA* [58, 80, 87].

Autonomic dysfunction (e.g. orthostatic hypotension, constipation, sweating, urinary, bowel and sexual dysfunction), as well as sleep disturbances, fatigue, and unexplained pain, were also found to be more frequent in PD patients with than those without *GBA* mutations [58, 80, 87, 104, 105].

Therapeutic considerations

While several reports suggested poor response to levodopa, majority of the studies found an excellent therapeutic effect of levodopa and dopamine agonists in PD-*GBA* [5, 56, 78, 84, 90]. DBS also had favorable outcome in PD-*GBA* patients, although these patients might require application of the procedure earlier in the course of the disease and might have faster cognitive decline and axial impairment after DBS [65, 99, 106, 107]. The enzyme replacement therapy for GD neither prevented development of PD, nor modified severity of symptoms and PD progression, probably due to a lack of passage of the enzyme across the blood–brain barrier [108–110]. Alternative therapy for GD is with miglustat, an iminosugar which inhibits the biosynthesis of macromolecular substrates that accumulate pathologically in glycosphingolipidoses [111]. Miglustat is able to cross blood–brain barrier but no clear data are available on the impact of miglustat on parkinsonism in GD patients [110, 112, 113].

Establishing the concept of *GBA*-related PD promoted a search for the pathogenic mechanisms through which GCase deficiency may influence pathogenesis of PD, suggesting that targeting the GCase–lysosomal pathway might be a rational approach for the "development of neuroprotective drugs in PD" [15].

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Compliance with ethical standards

Conflicts of interest Ivanka Marković and Nikola Kresojević report no disclosures. Vladimir Kostić received honoraria for lectures from Boehringer and Novartis and grants from Ministry of Education and Science, Republic of Serbia (Project #ON175090); Serbian Academy of Science and Arts, Novartis, Boehriner, Glaxo, Pfizer and Swisspharm. On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Sidransky E, Lopez G (2012) The link between the GBA gene and parkinsonism. Lancet Neurol 11(11):986–998. doi:10.1016/S1474-4422(12)70190-4
2. Brockmann K, Berg D (2014) The significance of GBA for Parkinson's disease. J Inherit Metab Dis 37(4):643–648. doi:10.1007/s10545-014-9714-7
3. Neudorfer O, Giladi N, Elstein D, Abrahamov A, Turezkite T, Aghai E et al (1996) Occurrence of Parkinson's syndrome in type I Gaucher disease. QJM 89(9):691–694. doi:10.1093/qjmed/89.9.691
4. Guimarães J, Amaral O, Sá Miranda MC (2003) Adult-onset neuronopathic form of Gaucher's disease: a case report. Parkinsonism Relat Disord 9(5):261–264. doi:10.1016/S1353-8020(02)00096-2
5. Aharon-Peretz J, Rosenbaum H, Gershoni-Baruch R (2004) Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews. N Engl J Med 351(19):1972–1977. doi:10.1056/NEJMoa033277
6. Lwin A, Orvisky E, Goker-Alpan O, LaMarca ME, Sidransky E (2004) Glucocerebrosidase mutations in subjects with parkinsonism. Mol Genet Metab 81(1):70–73. doi:10.1016/j.ymgme.2003.11.004
7. Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER et al (2009) Multicenter Analysis of Glucocerebrosidase Mutations in Parkinson's Disease. N Engl J Med 361(17):1651–1661. doi:10.1056/NEJMoa0901281
8. Brady RO, Kanfer JN, Shapiro D (1965) Metabolism of glucocerebrosides II. Evidence of an enzymatic deficiency in Gaucher's disease. Biochem Biophys Res Commun 18(2):221–225
9. Grabowski GA (2008) Phenotype, diagnosis, and treatment of Gaucher's disease. Lancet 372(9645):1263–1271. doi:10.1016/S0140-6736(08)61522-6
10. Wong K, Sidransky E, Verma A, Mixon T, Sandberg GD, Wakefield LK et al (2004) Neuropathology provides clues to the pathophysiology of Gaucher disease. Mol Genet Metab 82(3):192–207. doi:10.1016/j.ymgme.2004.04.011
11. Vitner EB, Farfel-Becker T, Eilam R, Biton I, Futerman AH (2012) Contribution of brain inflammation to neuronal cell death in neuronopathic forms of Gaucher's disease. Brain 135(Pt 6):1724–1735. doi:10.1093/brain/aws095
12. Burrow TA, Sun Y, Prada CE, Bailey L, Zhang W, Brewer A et al (2015) CNS, lung, and lymph node involvement in Gaucher disease type 3 after 11 years of therapy: clinical, histopathologic, and biochemical findings. Mol Genet Metab 114(2):233–241. doi:10.1016/j.ymgme.2014.08.011
13. Siebert M, Sidransky E, Westbroek W (2014) Glucocerebrosidase is shaking up the synucleinopathies. Brain 137:1304–1322. doi:10.1093/brain/awu002
14. Sardi SP, Cheng SH, Shihabuddin LS (2015) Gaucher-related synucleinopathies: the examination of sporadic neurodegeneration from a rare (disease) angle. Prog Neurobiol 125:47–62. doi:10.1016/j.pneurobio.2014.12.001
15. Schapira AH (2015) Glucocerebrosidase and Parkinson disease: recent advances. Mol Cell Neurosci 66:37–42. doi:10.1016/j.mcn.2015.03.013
16. Cullen V, Sardi SP, Ng J, Xu YH, Sun Y, Tomlinson JJ et al (2011) Acid β-glucosidase mutants linked to Gaucher disease, Parkinson disease, and Lewy body dementia alter α-synuclein processing. Ann Neurol 69(6):940–953. doi:10.1002/ana.22400
17. Gai WP, Yuan HX, Li XQ, Power JT, Blumbergs PC, Jensen PH (2000) In situ and in vitro study of colocalization and segregation of alpha-synuclein, ubiquitin, and lipids in Lewy bodies. Exp Neurol 166(2):324–333. doi:10.1006/exnr.2000.7527
18. Manning-Boğ AB, Schüle B, Langston JW (2009) Alpha-synuclein-glucocerebrosidase interactions in pharmacological Gaucher models: a biological link between Gaucher disease and parkinsonism. Neurotoxicology 30(6):1127–1132. doi:10.1016/j.neuro.2009.06.009
19. Argyriou A, Dermentzaki G, Papasilekas T, Moraitou M, Stamboulis E, Vekrellis K et al (2012) Increased dimerization of alpha-synuclein in erythrocytes in Gaucher disease and aging. Neurosci Lett 528(2):205–209. doi:10.1016/j.neulet.2012.08.069
20. Mazzulli JR, Xu YH, Sun Y, Knight AL, McLean PJ, Caldwell GA et al (2011) Gaucher Disease Glucocerebrosidase and α-Synuclein Form a Bidirectional Pathogenic Loop in Synucleinopathies. Cell 146(1):37–52. doi:10.1016/j.cell.2011.06.001
21. Sardi SP, Clarke J, Kinnecom C, Tamsett TJ, Li L, Stanek LM et al (2011) CNS expression of glucocerebrosidase corrects alpha-synuclein pathology and memory in a mouse model of Gaucher-related synucleinopathy. Proc Natl Acad Sci USA 108(29):12101–12106. doi:10.1073/pnas.1108197108
22. Murphy KE, Gysbers AM, Abbott SK, Tayebi N, Kim WS, Sidransky E et al (2014) Reduced glucocerebrosidase is associated with increased α-synuclein in sporadic Parkinson's disease. Brain 137(Pt 3):834–848. doi:10.1093/brain/awt367
23. Ron I, Horowitz M (2005) ER retention and degradation as the molecular basis underlying Gaucher disease heterogeneity. Hum Mol Genet 14(16):2387–2398. doi:10.1093/hmg/ddi240
24. Bendikov-Bar I, Ron I, Filocamo M, Horowitz M (2011) Characterization of the ERAD process of the L444P mutant glucocerebrosidase variant. Blood Cells Mol Dis 46(1):4–10. doi:10.1016/j.bcmd.2010.10.012
25. Bendikov-Bar I, Horowitz M (2012) Gaucher disease paradigm: from ERAD to comorbidity. Hum Mutat 33(10):1398–1407. doi:10.1002/humu.22124
26. Cooper AA, Gitler AD, Cashikar A, Haynes CM, Hill KJ, Bhullar B et al (2006) Alpha-Synuclein Blocks ER-Golgi Traffic and Rab1 Rescues Neuron Loss in Parkinson's Models. Science 313(5785):324–328. doi:10.1126/science.1129462
27. Thayanidhi N, Helm JR, Nycz DC, Bentley M, Liang Y, Hay JC et al (2010) Alpha-synuclein delays endoplasmic reticulum (ER)-to-Golgi transport in mammalian cells by antagonizing ER/Golgi SNAREs. Mol Biol Cell 21(11):1850–1863. doi:10.1091/mbc.E09-09-0801
28. Choi JH, Stubblefield B, Cookson MR, Goldin E, Velayati A, Tayebi N et al (2011) Aggregation of α-synuclein in brain samples from subjects with glucocerebrosidase mutations. Mol Genet Metab 104(1–2):185–188. doi:10.1016/j.ymgme.2011.06.008
29. Dermentzaki G, Dimitriou E, Xilouri M, Michelakakis H, Stefanis L (2013) Loss of β-Glucocerebrosidase Activity Does Not Affect Alpha-Synuclein Levels or Lysosomal Function in Neuronal Cells. PLoS ONE 8(4):e60674. doi:10.1371/journal.pone.0060674
30. Liu G, Chen M, Mi N, Yang W, Li X, Wang P et al (2015) Increased oligomerization and phosphorylation of α-synuclein are associated with decreased activity of glucocerebrosidase and protein phosphatase 2A in aging monkey brains. Neurobiol Aging 36(9):2649–2659. doi:10.1016/j.neurobiolaging.2015.06.004
31. Yap TL, Gruschus JM, Velayati A, Westbroek W, Goldin E, Moaven N et al (2011) Alpha-synuclein interacts with glucocerebrosidase providing a molecular link between Parkinson and Gaucher diseases. J Biol Chem 286(32):28080–28088. doi:10.1074/jbc.M111.237859
32. Yap TL, Velayati A, Sidransky E, Lee JC (2013) Membrane-bound α-synuclein interacts with glucocerebrosidase and

inhibits enzyme activity. Mol Genet Metab 108(1):56–64. doi:10.1016/j.ymgme.2012.11.010
33. Goker-Alpan O, Stubblefield BK, Giasson BI, Sidransky E (2010) Glucocerebrosidase is present in α-synuclein inclusions in Lewy body disorders. Acta Neuropathol 120(5):641–649. doi:10.1007/s00401-010-0741-7
34. Reczek D, Schwake M, Schröder J, Hughes H, Blanz J, Jin X et al (2007) LIMP-2 Is a Receptor for Lysosomal Mannose-6-Phosphate-Independent Targeting of β-Glucocerebrosidase. Cell 131(4):770–783. doi:10.1016/j.cell.2007.10.018
35. Gegg ME, Burke D, Heales SJ, Cooper JM, Hardy J, Wood NW et al (2012) Glucocerebrosidase deficiency in substantia nigra of parkinson disease brains. Ann Neuro 72(3):455–463. doi:10.1002/ana.23614
36. Rothaug M, Zunke F, Mazzulli JR, Schweizer M, Altmeppen H, Lüllmann-Rauch R et al (2014) LIMP-2 expression is critical for beta-glucocerebrosidase activity and alpha-synuclein clearance. Proc Natl Acad Sci USA 111(43):15573–15578. doi:10.1073/pnas.1405700111
37. Cuervo AM, Stefanis L, Fredenburg R, Lansbury PT, Sulzer D (2004) Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. Science 305(5688):1292–1295. doi:10.1126/science.1101738
38. Arias E, Cuervo AM (2011) Chaperone-mediated autophagy in protein quality control. Curr Opin Cell Biol 23(2):184–189. doi:10.1016/j.ceb.2010.10.009
39. Bandyopadhyay U, Kaushik S, Varticovski L, Cuervo AM (2008) The chaperone-mediated autophagy receptor organizes in dynamic protein complexes at the lysosomal membrane. Mol Cell Biol 28(18):5747–5763. doi:10.1128/MCB.02070-07
40. Kaushik S, Massey AC, Cuervo AM (2006) Lysosome membrane lipid microdomains: novel regulators of chaperone-mediated autophagy. EMBO J 25(17):3921–3933. doi:10.1038/sj.emboj.7601283
41. Hein LK, Duplock S, Hopwood JJ, Fuller M (2008) Lipid composition of microdomains is altered in a cell model of Gaucher disease. J Lipid Res 49(8):1725–1734. doi:10.1194/jlr.M800092-JLR200
42. Hattersley KJ, Hein LK, Fuller M (2013) Lipid composition of membrane rafts, isolated with and without detergent, from the spleen of a mouse model of Gaucher disease. Biochem Biophys Res Commun 442(1–2):62–67. doi:10.1016/j.bbrc.2013.11.009
43. Gan-Or Z, Dion PA, Rouleau GA (2015) Genetic perspective on the role of the autophagy-lysosome pathway in Parkinson disease. Autophagy 11(9):1443–1457. doi:10.1080/15548627.2015.1067364
44. Murphy KE, Gysbers AM, Abbott SK, Spiro AS, Furuta A, Cooper A et al (2015) Lysosomal-associated membrane protein 2 Isoforms Are Differentially Affected in Early Parkinson's Disease. Mov Disord 30(12):1639–1647. doi:10.1002/mds.26141
45. Rocha EM, Smith GA, Park E, Cao H, Brown E, Hallett P et al (2015) Progressive decline of glucocerebrosidase in aging and Parkinson's disease. Ann Clin Transl Neurol 2(4):433–438. doi:10.1002/acn3.177
46. Chiasserini D, Paciotti S, Eusebi P, Persichetti E, Tasegian A, Kurzawa-Akanbi M et al (2015) Selective loss of glucocerebrosidase activity in sporadic Parkinson's disease and dementia with Lewy bodies. Mol Neurodegener 10:15. doi:10.1186/s13024-015-0010-2
47. Bae EJ, Yang NY, Song M, Lee CS, Lee JS, Jung BC et al (2014) Glucocerebrosidase depletion enhances cell-to-cell transmission of α-synuclein. Nat Commun 5:4755. doi:10.1038/ncomms5755
48. El-Agnaf OM, Salem SA, Paleologou KE, Cooper LJ, Fullwood NJ, Gibson MJ et al (2003) Alpha-synuclein implicated in Parkinson's disease is present in extracellular biological fluids, including human plasma. FASEB J 17(13):1945–1947. doi:10.1096/fj.03-0098fje
49. Lee HJ, Patel S, Lee SJ (2005) Intravesicular Localization and Exocytosis of alpha-Synuclein and its Aggregates. J Neurosci 25(25):6016–6024. doi:10.1523/JNEUROSCI.0692-05.2005
50. Lee HJ, Suk JE, Patrick C, Bae EJ, Cho JH, Rho S et al (2010) Direct Transfer of alpha-Synuclein from Neuron to Astroglia Causes Inflammatory Responses in Synucleinopathies. J Biol Chem 285(12):9262–9272. doi:10.1074/jbc.M109.081125
51. Emmanouilidou E, Melachroinou K, Roumeliotis T, Garbis SD, Ntzouni M, Margaritis LH et al (2010) Cell-Produced alpha-Synuclein Is Secreted in a Calcium-Dependent Manner by Exosomes and Impacts Neuronal Survival. J Neurosci 30(20):6838–6851. doi:10.1523/JNEUROSCI.5699-09.2010
52. Emmanouilidou E, Elenis D, Papasilekas T, Stranjalis G, Gerozissis K, Ioannou PC et al (2011) Assessment of alpha-Synuclein Secretion in Mouse and Human Brain Parenchyma. PLoS ONE 6(7):e22225. doi:10.1371/journal.pone.0022225
53. Dulovic M, Jovanovic M, Xilouri M, Stefanis L, Harhaji-Trajkovic L, Kravic-Stevovic T et al (2014) The protective role of AMP-activated protein kinase in alpha-synuclein neurotoxicity in vitro. Neurobiol Dis 63:1–11. doi:10.1016/j.nbd.2013.11.002
54. Alvarez-Erviti L, Seow Y, Schapira AH, Gardiner C, Sargent IL, Wood MJ et al (2011) Lysosomal dysfunction increases exosome-mediated alpha-synuclein release and transmission. Neurobiol Dis 42(3):360–367. doi:10.1016/j.nbd.2011.01.029
55. Lee HJ, Bae EJ, Lee SJ (2014) Extracellular alpha–synuclein- a novel and crucial factor in Lewy body diseases. Nat Rev Neurol 10(2):92–98. doi:10.1038/nrneurol.2013.275
56. Kumar KR, Ramirez A, Göbel A, Kresojević N, Svetel M, Lohmann K et al (2013) Glucocerebrosidase mutations in a Serbian Parkinson's disease population. Eur J Neurol 20(2):402–405. doi:10.1111/j.1468-1331.2012.03817.x
57. Lesage S, Anheim M, Condroyer C, Pollak P, Durif F, Dupuits C et al (2011) Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet 20(1):202–210. doi:10.1093/hmg/ddq454
58. McNeill A, Duran R, Hughes DA, Mehta A, Schapira AH (2012) A clinical and family history study of Parkinson's disease in heterozygous glucocerebrosidase mutation carriers. J Neurol Neurosurg Psychiatry 83(8):853–854. doi:10.1136/jnnp-2012-302402
59. Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH et al (2009) Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 132(Pt 7):1783–1794. doi:10.1093/brain/awp044
60. Choi JM, Kim WC, Lyoo CH, Kang SY, Lee PH, Baik JS et al (2012) Association of mutations in the glucocerebrosidase gene with Parkinson disease in a Korean population. Neurosci Lett 514(1):12–15. doi:10.1016/j.neulet.2012.02.035
61. Toft M, Pielsticker L, Ross OA, Aasly JO, Farrer MJ (2006) Glucocerebrosidase gene mutations and Parkinson disease in the Norwegian. Neurology 66(3):415–417
62. Nishioka K, Vilariño-Güell C, Cobb SA, Kachergus JM, Ross OA, Wider C et al (2011) Glucocerebrosidase mutations are not a common risk factor for Parkinson disease in North Africa. Neurosci Lett 477(2):57–60. doi:10.1016/j.neulet.2009.11.066
63. Zokaei N, McNeill A, Proukakis C, Beavan M, Jarman P, Korlipara P et al (2014) Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain 137(Pt 8):2303–2311. doi:10.1093/brain/awu143
64. Bultron G, Kacena K, Pearson D, Boxer M, Yang R, Sathe S et al (2010) The risk of Parkinson's disease in type 1 Gaucher disease. J Inherit Metab Dis 33(2):167–173. doi:10.1007/s10545-010-9055-0

65. Chetrit EB, Alcalay RN, Steiner-Birmanns B, Altarescu G, Phillips M, Elstein D et al (2013) Phenotype in patients with Gaucher disease and Parkinson disease. Blood Cells Mol Dis 50(3):218–221. doi:10.1016/j.bcmd.2012.11.011
66. Gan-Or Z, Giladi N, Orr-Urtreger A (2009) Differential phenotype in Parkinson's disease patients with severe versus mild GBA mutations. Brain 132(Pt 10):e125. doi:10.1093/brain/awp161
67. Gan-Or Z, Amshalom I, Kilarski LL, Bar-Shira A, Gana-Weisz M, Mirelman A et al (2015) Differential effects of severe vs mild GBA mutations on Parkinson disease. Neurology 84(9):880–887. doi:10.1212/WNL.0000000000001315
68. Alcalay RN, Dinur T, Quinn T, Sakanaka K, Levy O, Waters C et al (2014) Comparison of Parkinson Risk in Ashkenazi Jewish Patients With Gaucher Disease and GBA Heterozygotes. JAMA Neurol 71(6):752–757. doi:10.1001/jamaneurol.2014.313
69. Rana HQ, Balwani M, Bier L, Alcalay RN (2013) Age-specific Parkinson disease risk in GBA mutation carriers: information for genetic counseling. Genet Med 15(2):146–149. doi:10.1038/gim.2012.107
70. Anheim M, Elbaz A, Lesage S, Durr A, Condroyer C, Viallet F et al (2012) Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. Neurology 78(6):417–420. doi:10.1212/WNL.0b013e318245f476
71. Giraldo P, Capablo JL, Alfonso P, Garcia-Rodriguez B, Latre P, Irun P et al (2011) Neurological manifestations in patients with Gaucher disease and their relatives, it is just a coincidence? J Inherit Metab Dis 34(3):781–787. doi:10.1007/s10545-011-9298-4
72. Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E (2004) Parkinsonism among Gaucher disease carriers. J Med Genet 41(12):937–940. doi:10.1136/jmg.2004.024455
73. Halperin A, Elstein D, Zimran A (2006) Increased incidence of Parkinson disease among relatives of patients with Gaucher disease. Blood Cells Mol Dis 36(3):426–428. doi:10.1016/j.bcmd.2006.02.004
74. Tan EK, Tong J, Fook-Chong S, Yih Y, Wong MC, Pavanni R et al (2007) Glucocerebrosidase Mutations and Risk of Parkinson Disease in Chinese Patients. Arch Neurol 64(7):1056–1058. doi:10.1001/archneur.64.7.1056
75. Wu YR, Chen CM, Chao CY, Ro LS, Lyu RK, Chang KH et al (2007) Glucocerebrosidase gene mutation is a risk factor for early onset of Parkinson disease among Taiwanese. J Neurol Neurosurg Psychiatry 78(9):977–979. doi:10.1136/jnnp.2006.105940
76. Clark LN, Ross BM, Wang Y, Mejia-Santana H, Harris J, Louis ED et al (2007) Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. Neurology 69(12):1270–1277. doi:10.1212/01.wnl.0000276989.17578.02
77. Nichols WC, Pankratz N, Marek DK, Pauciulo MW, Elsaesser VE, Halter CA et al (2009) Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. Neurology 72(4):310–316. doi:10.1212/01.wnl.0000327823.81237.d1
78. Setó-Salvia N, Pagonabarraga J, Houlden H, Pascual-Sedano B, Dols-Icardo O, Tucci A et al (2012) Glucocerebrosidase Mutations Confer a Greater Risk of Dementia during Parkinson's Disease Course. Mov Disord 27(3):393–399. doi:10.1002/mds.24045
79. Winder-Rhodes SE, Evans JR, Ban M, Mason SL, Williams-Gray CH, Foltynie T et al (2013) Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 136(Pt 2):392–399. doi:10.1093/brain/aws318
80. Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T et al (2011) GBA-associated PD presents with nonmotor characteristics. Neurology 77(3):276–280. doi:10.1212/WNL.0b013e318225ab77
81. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH (2015) Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol 72(2):201–208. doi:10.1001/jamaneurol.2014.2950
82. McNeill A, Duran R, Proukakis C, Bras J, Hughes D, Mehta A et al (2012) Hyposmia and cognitive impairment in Gaucher disease patients and carriers. Mov Disord 27(4):526–532. doi:10.1002/mds.24945
83. Gan-Or Z, Mirelman A, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y et al (2015) GBA mutations are associated with Rapid Eye Movement Sleep Behavior Disorder. Ann Clin Transl Neurol 2(9):941–945. doi:10.1002/acn3.228
84. Sato C, Morgan A, Lang AE, Salehi-Rad S, Kawarai T, Meng Y et al (2005) Analysis of the glucocerebrosidase gene in Parkinson's disease. Mov Disord 20(3):367–370. doi:10.1002/mds.20319
85. Machaczka M, Rucinska M, Skotnicki AB, Jurczak W (1999) Parkinson's Syndrome Preceding Clinical Manifestation of Gaucher's Disease. Am J Hematol 61(3):216–217. doi:10.1002/(SICI)1096-8652(199907)61:3<216:AID-AJH11>3.0.CO;2-E
86. Kresojević N, Janković M, Petrović I, Kumar KR, Dragašević N, Dobričić V et al (2015) Presenting symptoms of GBA-related Parkinson's disease. Parkinsonism Relat Disord 21(7):804–807. doi:10.1016/j.parkreldis.2015.04.028
87. Wang C, Cai Y, Gu Z, Ma J, Zheng Z, Tang BS et al (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(3):725.e1–725.e6. doi:10.1016/j.neurobiolaging.2013.08.012
88. Mao XY, Burgunder JM, Zhang ZJ, An XK, Zhang JH, Yang Y et al (2010) Association between GBA L444P mutation and sporadic Parkinson's disease from Mainland China. Neurosci Lett 469(2):256–259. doi:10.1016/j.neulet.2009.12.007
89. Gan-Or Z, Giladi N, Rozovski U, Shifrin C, Rosner S, Gurevich T, Bar-Shira A et al (2008) Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology 70(24):2277–2283. doi:10.1212/01.wnl.0000304039.11891.29
90. Pulkes T, Choubtum L, Chitphuk S, Thakkinstian A, Pongpakdee S, Kulkantrakorn K et al (2014) Glucocerebrosidase mutations in Thai patients with Parkinson's disease. Parkinsonism Relat Disord 20(9):986–991. doi:10.1016/j.parkreldis.2014.06.007
91. Socal MP, Bock H, Michelin-Tirelli K, Hilbig A, Saraiva-Pereira ML, Rieder CR et al (2009) Parkinson's disease and the heterozygous state for glucocerebrosidase mutations among Brazilians. Parkinsonism Relat Disord 15(1):76–78. doi:10.1016/j.parkreldis.2008.01.019
92. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E (2008) The spectrum of Parkinsonian manifestations associated with glucocerebrosidase mutations. Arch Neurol 65(10):1353–1357. doi:10.1001/archneur.65.10.1353
93. Huang CL, Wu-Chou YH, Lai SC, Chang HC, Yeh TH, Weng YH et al (2011) Contribution of glucocerebrosidase mutation in a large cohort of sporadic Parkinson's disease in Taiwan. Eur J Neurol 18(10):1227–1232. doi:10.1111/j.1468-1331.2011.03362.x
94. Li Y, Sekine T, Funayama M, Li L, Yoshino H, Nishioka K et al (2014) Clinicogenetic study of GBA mutations in patients with familial Parkinson's disease. Neurobiol Aging 35(4):935.e3–935.e8. doi:10.1016/j.neurobiolaging.2013.09.019

95. Aharon-Peretz J, Badarny S, Rosenbaum H, Gershoni-Baruch R (2005) Mutations in the glucocerebrosidase gene and Parkinson disease: phenotype-genotype correlation. Neurology 65(9):1460–1461. doi:10.1212/01.wnl.0000176987.47875.28
96. Oeda T, Umemura A, Mori Y, Tomita S, Kohsaka M, Park K et al (2015) Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. Neurobiol Aging 36(12):3306–3313. doi:10.1016/j.neurobiolaging.2015.08.027
97. Davis AA, Andruska KM, Benitez BA, Racette BA, Perlmutter JS, Cruchaga C (2015) Variants in GBA, SNCA, and MAPT Influence Parkinson Disease Risk, Age at Onset, and Progression. Neurobiol Aging 37:209.e1–209.e7. doi:10.1016/j.neurobiolaging.2015.09.014
98. Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W et al (2015) GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord 30(3):407–411. doi:10.1002/mds.26071
99. Angeli A, Mencacci NE, Duran R, Aviles-Olmos I, Kefalopoulou Z, Candelario J et al (2013) Genotype and phenotype in Parkinson's disease: lessons in heterogeneity from deep brain stimulation. Mov Disord 28(10):1370–1375. doi:10.1002/mds.25535
100. Mitsui J, Mizuta I, Toyoda A, Ashida R, Takahashi Y, Goto J et al (2009) Mutations for Gaucher disease confer high susceptibility to Parkinson disease. Arch Neurol 66(5):571–576. doi:10.1001/archneurol.2009.72
101. Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M et al (2012) Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology 78(18):1434–1440. doi:10.1212/WNL.0b013e318253d54b
102. Malec-Litwinowicz M, Rudzińska M, Szubiga M, Michalski M, Tomaszewski T, Szczudlik A (2014) Cognitive impairment in carriers of glucocerebrosidase gene mutation in Parkinson disease patients. Neurol Neurochir Pol 48(4):258–261. doi:10.1016/j.pjnns.2014.07.005
103. Kresojević N, Mijajlović M, Perić S, Pavlović A, Svetel M, Janković M et al (2013) Transcranial sonography in patients with Parkinson's disease with glucocerebrosidase mutations. Parkinsonism Relat Disord 19(4):431–435. doi:10.1016/j.parkreldis.2012.12.006
104. Goker-Alpan O, Lopez G, Vithayathil J, Davis J, Hallett M, Sidransky E (2008) The spectrum of Parkinsonian Manifestations associated with glucocerebrosidase mutations. Arch Neurol 65(10):1353–1357. doi:10.1001/archneur.65.10.1353
105. Böttcher T, Rolfs A, Meyer B, Grossmann A, Berg D, Kropp P et al (2013) Clinical, genetic, and brain sonographic features related to Parkinson's disease in Gaucher disease. J Neurol 260(10):2523–2531. doi:10.1007/s00415-013-7011-2
106. Weiss D, Brockmann K, Srulijes K, Meisner C, Klotz R, Reinbold S et al (2012) Long-term follow-up of subthalamic nucleus stimulation in glucocerebrosidase-associated Parkinson's disease. J Neurol 259(9):1970–1972. doi:10.1007/s00415-012-6469-7
107. Kono S, Ouchi Y, Terada T, Ida H, Suzuki M, Miyajima H (2010) Functional brain imaging in glucocerebrosidase mutation carriers with and without parkinsonism. Mov Disord 25(12):1823–1829. doi:10.1002/mds.23213
108. Rosenbloom B, Balwani M, Bronstein JM, Kolodny E, Sathe S, Gwosdow AR et al (2011) The incidence of parkinsonism in patients with type 1 Gaucher disease: data from the ICGG Gaucher Registry. Blood Cells Mol Dis 46(1):95–102. doi:10.1016/j.bcmd.2010.10.006
109. Bembi B, Zambito Marsala S, Sidransky E, Ciana G, Carrozzi M, Zorzon M et al (2003) Gaucher's disease with Parkinson's disease: clinical and pathological aspects. Neurology 61(1):99–101
110. Kraoua I, Stirnemann J, Ribeiro MJ, Rouaud T, Verin M, Annic A et al (2009) Parkinsonism in Gaucher's disease type 1: ten new cases and a review of the literature. Mov Disord 24(10):1524–1530. doi:10.1002/mds.22593
111. Cox TM, Aerts JM, Andria G, Beck M, Belmatoug N, Bembi B et al (2003) The role of the iminosugar N-butyldeoxynojirmycin (miglustat) in the management of type I (non-neuronopathic) Gaucher disease: a position statement. J Inherit Metab Dis 26(6):513–526. doi:10.1023/A:1025902113005
112. Goker-Alpan O, Sidransky E (2008) Treating patients with Gaucher disease and parkinsonism: misrepresentation in a title. Parkinsonism Relat Disord 14(1):81–82
113. Hughes DA, Ginsberg L, Baker R, Goodwin S, Milligan A, Richfield L et al (2007) Effective treatment of an elderly patient with Gaucher's disease and parkinsonism: a case report of 24 months' oral substrate reduction therapy with miglustat. Parkinsonism Relat Disord 13(6):365–368. doi:10.1016/j.parkreldis.2006.07.010
114. Clark LN, Nicolai A, Afridi S, Harris J, Mejia-Santana H, Strug L et al (2005) Pilot association study of the beta-glucocerebrosidase N370S allele and Parkinson's disease in subjects of Jewish ethnicity. Mov Disord 20(1):100–103. doi:10.1002/mds.20320
115. De Marco EV, Annesi G, Tarantino P, Rocca FE, Provenzano G, Civitelli D et al (2008) Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy. Mov Disord 23(3):460–463. doi:10.1002/mds.21892
116. Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC et al (2008) Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol 65(3):379–382. doi:10.1001/archneurol.2007.68
117. Kalinderi K, Bostantjopoulou S, Paisan-Ruiz C, Katsarou Z, Hardy J, Fidani L (2009) Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Greece. Neurosci Lett 452(2):87–89. doi:10.1016/j.neulet.2009.01.029
118. Bras J, Paisan-Ruiz C, Guerreiro R, Ribeiro MH, Morgadinho A, Januario C et al (2010) Complete screening for glucocerebrosidase mutations in parkinson disease patients from Portugal. Neurobiol Aging 30(9):1515–1517. doi:10.1016/j.neurobiolaging.2007.11.016
119. Sun QY, Guo JF, Wang L, Yu RH, Zuo X, Yao LY et al (2010) Glucocerebrosidase gene L444P mutation is a risk factor for Parkinson's disease in Chinese population. Mov Disord 25(8):1005–1011. doi:10.1002/mds.23009
120. Hu FY, Xi J, Guo J, Yu LH, Liu L, He XH et al (2010) Association of the glucocerebrosidase N370S allele with Parkinson's disease in two separate Chinese Han populations of mainland China. Eur J Neurol 17(12):1476–1478. doi:10.1111/j.1468-1331.2010.03097.x
121. Lesage S, Condroyer C, Hecham N, Anheim M, Belarbi S, Lohman E et al (2011) Mutations in the glucocerebrosidase gene confer a risk for parkinson disease in north Africa. Neurology 76(3):301–303. doi:10.1212/WNL.0b013e318207b01e
122. Moraitou M, Hadjigeorgiou G, Monopolis I, Dardiotis E, Bozi M, Vassilatis D et al (2011) β-Glucocerebrosidase gene mutations in two cohorts of Greek patients with sporadic Parkinson's disease. Mol Genet Metab 104(1–2):149–152. doi:10.1016/j.ymgme.2011.06.015
123. Noreau A, Rivière JB, Diab S, Dion PA, Panisset M, Soland V et al (2011) Glucocerebrosidase mutations in a French-Canadian Parkinson's disease cohort. Can J Neurol Sci 38(5):772–773

124. Emelyanov A, Boukina T, Yakimovskii A, Usenko T, Drosdova A, Zakharchuk A et al (2012) Glucocerebrosidase Gene Mutations Are Associated with Parkinson's Disease in Russia. Mov Disord 27(1):158–159. doi:10.1002/mds.23950
125. Guimarães Bde C, Pereira AC, Rodrigues Fda C, dos Santos AV, Campos M Jr, dos Santos JM et al (2012) Glucocerebrosidase N370S and L444P mutations as risk factors for Parkinson's disease in Brazilian patients. Parkinsonism Relat Disord 18(5):688–689. doi:10.1016/j.parkreldis.2011.11.028
126. Wang Y, Liu L, Xiong J, Zhang X, Chen Z, Yu L, Chen C et al (2012) Glucocerebrosidase L444P mutation confers genetic risk for Parkinson's disease in central China. Behav Brain Funct 8:57. doi:10.1186/1744-9081-8-57
127. Zhang X, Bao QQ, Zhuang XS, Gan SR, Zhao D, Liu Y et al (2012) Association of common variants in the glucocerebrosidase gene with high susceptibility to Parkinson's disease among chinese. Chin J Physiol 55(6):398–404. doi:10.4077/CJP.2011.AMM076
128. González-Del Rincón Mde L, Monroy Jaramillo N, Suárez Martínez AI, Yescas Gómez P, Boll Woehrlen MC, López López M et al (2013) The L444P GBA mutation is associated with early-onset Parkinson's disease in Mexican Mestizos. Clin Genet 84(4):386–387. doi:10.1111/cge.12084
129. Yu Z, Wang T, Xu J, Wang W, Wang G, Chen C et al (2015) Mutations in the glucocerebrosidase gene are responsible for Chinese patients with Parkinson's disease. J Hum Genet 60(2):85–90. doi:10.1038/jhg.2014.110
130. Asselta R, Rimoldi V, Siri C, Cilia R, Guella I, Tesei S et al (2014) Glucocerebrosidase mutations in primary parkinsonism. Parkinsonism Relat Disord 20(11):1215–1220. doi:10.1016/j.parkreldis.2014.09.003
131. Han F, Grimes DA, Li F, Wang T, Yu Z, Song N et al (2016) Mutations in the glucocerebrosidase gene are common in patients with Parkinson's disease from Eastern Canada. Int J Neurosci 126(5):415–421. doi:10.3109/00207454.2015.1023436