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The association between β -glucocerebrosidase mutations and parkinsonism

Matthew Swan, MD and Rachel Saunders-Pullman, MD, MPH

Department of Neurology, Beth Israel Medical Center, New York, NY

Abstract

Mutations in the β -glucocerebrosidase gene (GBA), which encodes the lysosomal enzyme β -glucocerebrosidase, have traditionally been implicated in Gaucher disease, an autosomal-recessive lysosomal storage disorder. Yet the past two decades have yielded an explosion of epidemiological and basic-science evidence linking mutations in GBA with the development of Parkinson disease as well. Although the specific contribution of mutant GBA to the pathogenesis of parkinsonism remains unknown, evidence suggests both loss of function and toxic gain-of-function by abnormal β -glucocerebrosidase may be important, and a close relationship between β -glucocerebrosidase and α -synuclein. Furthermore, multiple lines of evidence suggest that while GBA-associated PD closely mimics idiopathic PD (IPD), it may present at a younger age, and is more frequently complicated by cognitive dysfunction. Understanding the clinical association between GBA and PD, and the relationship between β -glucocerebrosidase and α -synuclein, may enhance understanding of the pathogenesis of IPD, improve prognostication and treatment of GBA carriers with parkinsonism, and may furthermore inform therapies for IPD not due to GBA mutations.

Keywords

Parkinson disease; parkinsonism; dementia with Lewy bodies; Gaucher disease; GBA; β -glucocerebrosidase

Introduction: A role for GBA mutations beyond autosomal recessive Gaucher disease

Traditional understanding of autosomal recessive disorders is that the pathological phenotype is present in the homozygous or compound heterozygous state, and that heterozygous carriers do not develop disease. Recently, however, multiple autosomal recessive alleles have been found to confer a risk of disease in the heterozygous state. An example is the increased risk of malignancies in ataxia telangiectasia, not only in homozygotes, but possibly in heterozygote carriers as well¹. Similarly, only recently have investigators demonstrated an indisputable association between GBA, the gene that is implicated in the lysosomal storage disorder Gaucher disease, and parkinsonism. Gaucher

Corresponding author: Matthew Swan, MD 10 Union Square East, Suite 5K New York, NY 10003 matswan@chnpnet.org.

Compliance with Ethics Guidelines

Conflict of Interest

Matthew Swan declares no potential conflicts of interest relevant to this article.

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Human and Animal Rights and Informed Consent

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disease (GD), while rare, is the most common lysosomal storage disorder worldwide². It results from homozygosity or compound heterozygosity for mutations in GBA, which encodes the lysosomal enzyme β -glucocerebrosidase (also known as acid β -glucosidase). Abnormal β -glucocerebrosidase results in accumulation of glycolipid substrates in the lysosomes of reticulo-endothelial cells, leading to a variety of systemic manifestations, including organomegaly, anemia, thrombocytopenia, and bone disease. Gaucher disease has historically been classified by whether it involves the nervous system (types 2 and 3) or not (type 1); however, ongoing study of its phenotypic heterogeneity has led to arguments that this classification is too simple to encompass what is actually a wide spectrum of clinical manifestations². Indeed, the initial observations of parkinsonism in patients with Gaucher disease were in those with the so-called non-neuronopathic type 1 (GD1)³. While types 2 and 3 typically begin in infancy or childhood, respectively, and present fairly severe clinical disease, type 1 may present anytime from childhood to adulthood, and may remain asymptomatic and go undiagnosed. Accordingly, some cases of GD1 were only discovered through research studies of Parkinson disease probands⁴.

Mutations in GBA are the most common genetic contributor to parkinsonism described to date⁵⁻⁷. As the association between GBA and parkinsonism overall was itself only recently established, the phenotypic range of GBA-related parkinsonism is still being delineated. GBA-related parkinsonism usually mimics idiopathic Parkinson's Disease (IPD), but it has also been characterized by more prominent cognitive impairment in a subset⁸ of cases, with widespread Lewy body pathology that may more closely resemble late IPD or diffuse Lewy body disease (DLB)⁹. The effect of a GBA mutation may be mutation-specific: for example, "mild" GBA mutations confer about twice the risk of developing parkinsonism to carriers compared to non-carriers, whereas "severe" mutations confer up to 13 times the risk¹⁰. Furthermore, unlike other PD-related genes such as LRRK2 and the α -synuclein gene SNCA, which are viewed as causal (albeit with reduced penetrance), there is debate as to whether GBA mutations as a group should be considered dominant causal genes or susceptibility mutations¹¹. Ultimately, they may represent both, and it may be most accurate to consider the mutations as "causal but complex," falling outside the simple Mendelian paradigm (see figure 1).

Understanding the clinical and genetic issues surrounding GBA-related parkinsonism informs clinical care, including genetic counseling, and research. In this review, we will explore the background, pathophysiology, pathology and clinical implications of the complex relationship between β -glucocerebrosidase mutations and parkinsonism, including a putative role for β -glucocerebrosidase in IPD as well.

The evidence linking GBA and parkinsonism

Parkinsonism in GD patients

In the 1990s, reports on patients with GD1 who also had concomitant parkinsonism emerged. Neudorfer et al described six patients with otherwise classic GD1, who developed parkinsonism at a mean age of 49 years, and who presented with atypical features: two had severe psychiatric symptoms, including depression and psychosis; one had myoclonus; and four were unresponsive to levodopa therapy³. Tayebi et al described a woman with mild GD1 due to compound heterozygosity for the GBA mutations L444P and D406H, who developed left hand tremor at age 42, followed by progressive left-sided rigidity and gait deterioration, and atypical features such as supranuclear ophthalmoplegia, retrocollis, myoclonus, upper motor neuron signs, and progressive confusion¹². A later series described additional GD1 patients with atypical parkinsonism beginning in their 40s, a third of whom had dementia, and two of whom had slowed horizontal saccadic eye movements¹³. Yet the apparent pattern of atypical parkinsonism in GD1 patients was not universal and a paper

followed of four GD1 patients with a more typical, levodopa-responsive PD phenotype¹⁴. More recent assessments of large Gaucher cohorts have underscored the high susceptibility for PD among patients with GD1, estimating the lifetime relative risk of developing PD among GD1 patients to be 21.4 times that of the general population¹⁵, and the probability that a GD1 will develop parkinsonism to be 5-7% before age 70, and 9-12% before age 80¹⁶.

Pathological evidence

Post-mortem microscopic examination of the brains of GD1 patients with parkinsonism demonstrated substantia nigra neuronal Lewy bodies and loss of pigmented neurons, similar to IPD¹³. Lewy bodies were also present in hippocampal pyramidal cell layers CA2-4 in the brains of GD1 patients with parkinsonism,¹⁷ and these cell layers are selectively involved in only a few other conditions including, notably, dementia with Lewy bodies¹⁷. In addition, GD1 patients without parkinsonism displayed astrogliosis in these hippocampal layers, suggesting that some aspect of GD pathophysiology selectively targets these cells, and that their involvement is likely not due to coincident DLB or IPD¹⁷. Further, α -synuclein oligomers similar to those seen in synucleinopathies such as advanced IPD and DLB are also observed in cortical tissue of GBA heterozygotes with parkinsonism and GD1⁹; however, it is debated whether GBA-related parkinsonism results in a higher burden of Lewy body pathology than IPD¹⁸.

Parkinsonism in Gaucher families and GBA heterozygotes; GBA mutations in PD clinics

The high prevalence of parkinsonism among obligate GBA carriers¹⁹ led to a search for GBA mutations among IPD patients. Analysis of 57 subjects with pathologically-confirmed IPD found that 21% harbored a GBA mutation²⁰. Among Ashkenazi Jewish (AJ) patients with PD, 31.3% were found to carry GBA mutations, as opposed to 6.2% of controls²¹. The percentage of GBA mutation carriers has been slightly lower in other AJ PD cohorts, but the association between GBA and IPD in Ashkenazim remains robust^{10, 22}. While it was initially unclear whether GBA mutations conferred an epidemiologically significant risk for IPD in other ethnic populations, the association between GBA mutations and IPD has been confirmed worldwide^{23, 24}, although the predominant mutations and the magnitude of epidemiological risk varies from population to population^{5-7, 25-39}.

GBA-PD: is there a distinct phenotype nested within a wide phenotypic spectrum?

Early reports of GD1 patients with parkinsonism described a range of phenotypes, from a classic IPD picture, to the atypical presentations described above^{3, 12, 13}. Although GBA-associated PD is often indistinguishable from IPD, emerging research suggests subtle differences (see table 1). One small study showed no difference between GBA-PD and IPD patients in age of onset, risk of dementia, levodopa responsiveness, or prevalence of different parkinsonian motor signs at initial evaluation⁴⁰, but GBA-PD patients were more likely to have symmetrical onset of motor manifestations (27.5%, vs. 8.1% in IPD), and were slightly less likely to present with tremor (70.3%, versus 86.5% in IPD patients). A larger study found GBA-PD patients were more likely than IPD and LRRK2-PD patients to present initially with bradykinesia⁴¹, an observation that was replicated in a large European study⁷. Yet other studies have not clearly identified motor differences between IPD and GBA-PD patients²².

Whether GBA mutations affect the age of onset of PD remains disputed. Some studies have found that GBA mutations result in a later age of onset³² or have no impact^{7, 29}, but the majority demonstrate an earlier onset of PD symptoms in mutant GBA carriers^{25, 27, 35, 36, 38, 42}. One group found that the mean age of symptom onset in GBA and

LRRK2 carriers is younger than in IPD (55 and 57 years, respectively, vs. 61 years)¹⁰, and that the percentage with early-onset (that is, onset at <50 years of age) is higher in GBA-PD (19% vs. 15% in non-carriers)⁴¹. Although many studies suggest that GBA carriers have slightly younger age at onset, and that they may be overrepresented in early-onset groups²², in most studies, the average age of onset of GBA-related PD remains between 50 and 60. Severity of GBA mutations may impact on age of PD onset as well (see below).

Impaired cognition

While GBA-associated PD as a whole, including GBA-PD and GD1-PD, does not usually present with predominant cognitive dysfunction, the most prominent atypical subgroup of GBA-PD resembles dementia with Lewy bodies (DLB) with early cognitive impairment, or Parkinson disease with dementia (PDD). The possibility that GBA mutations might confer a greater burden of cognitive impairment was suggested by the finding of hippocampal gliosis and Lewy bodies in GD1 patients¹⁷ and by a study of GBA-PD heterozygotes, two-thirds of whom had varying degrees of cortical and hippocampal Lewy bodies²⁰. In a group of PD patients who were first diagnosed with GD1 after genetic screening for research, we reported a phenotype with prominent development of cognitive impairment and cognitive fluctuations, variably complicated by depression, anxiety, and a propensity for medication-induced hallucinations⁴. GBA mutations have also been implicated in dementia with Lewy bodies. In one study of autopsied brains with synucleinopathies, 23% of DLB subjects carried GBA mutations⁴³. A later neuropathological study found that 28% of DLB brains had GBA mutations, compared to 10% of Alzheimer disease brains, and 1% of controls. Furthermore, the presence of a GBA mutation was associated with a greater likelihood of having cortical Lewy bodies⁴⁴. A large clinical study looked for the presence of N370S and L444P mutant GBA alleles in PD patients, healthy controls, and DLB patients, and found GBA mutations were over 6 times as frequent in both PD and DLB cohorts compared to controls⁴⁵.

A retrospective study of PD patients found cognitive impairment, including dementia, in 48% of GBA carriers, as well as a higher burden of cortical Lewy body pathology⁵. GBA-PD patients are more likely than IPD patients to report subjective cognitive impairment as screened in Part I of the United Parkinson's Disease Rating Scale (UPDRS)⁴⁶, and a handful of studies have demonstrated clear objective cognitive impairment in GBA-PD. One showed that GBA-PD patients score lower than IPD patients on the Montreal Cognitive Assessment (MoCA)⁴⁷. Another found that GBA-PD patients perform significantly worse on visuospatial and memory tasks, particularly non-verbal memory tasks, compared to IPD patients, and are more likely to meet criteria for mild cognitive impairment (MCI) or dementia than IPD⁸. Indeed, mutations in GBA confer a six-fold increased risk of developing dementia during the course of PD⁴⁸.

Despite all of these findings, research may be biased away from detecting cognitive impairment in GBA-PD, as recruitment comes from source populations with a focus on PD, not parkinsonism more generally. A small study of patients with parkinsonism and GBA mutations found a wide range of clinical manifestations, from an akinetic type of PD to a clinical picture similar to that of DLB⁴⁹, raising the question of whether studies of GBA mutations should seek to broaden enrollment criteria, as prominent early cognitive features may preclude inclusion in PD studies.

Hallucinations, apathy, anxiety, and depression

The burden of depression and other neuropsychiatric symptoms such as apathy, anxiety, and sleep disruption, may be greater in GBA-associated PD⁴⁷. In GD1 patients with PD, we found that visual hallucinations were a complication of therapy in all subjects⁴. Others found

that 45% of GBA-PD subjects developed visual hallucinations not related to treatment, on average about 10 years after motor symptom onset⁵. Another recent study found that, while GBA-PD patients are as likely as IPD patients to experience hallucinations at least once during their disease course, they are much more likely to experience persistent hallucinations, with 26.5% of GBA carriers having hallucinations for more than 6 months, compared to only 6.7% of non-carriers⁵⁰.

Non-motor features

Studies in both GD1-PD and heterozygous GBA-PD suggest prominent olfactory dysfunction in GBA-related PD^{4, 41}. Olfaction may be as^{8, 47} or possibly more prominently affected in GBA-PD compared with IPD. Dysautonomia also appears to be part of the phenotypic spectrum of GBA-associated parkinsonism⁴⁶.

Neuroimaging in GBA-PD

Transcranial sonography (TCS)

TCS is a relatively inexpensive modality that demonstrates hyperechogenicity of the substantia nigra in approximately 90% of PD patients and 10-15% of controls⁵¹. Nigral hyperechogenicity is observed in GD1 patients with PD, and is similar to that seen in DLB, IPD and PDD⁴. It is also seen in heterozygous GBA carriers with PD^{46, 52}, and gene dose (one vs. two GBA mutations) did not affect the degree of nigral echogenicity⁵². Interestingly, TCS in GD1 patients without PD is normal⁵³. Hypoechogenicity of the brainstem raphe, reported in PD with depression⁵¹, may reflect structural damage to the serotonergic system, and is more prevalent in PD patients with GBA mutations compared to IPD patients^{46, 53} and to controls⁵³, and may correspond with the increased rate of depression among GBA-PD⁴⁶.

Functional neuroimaging

Positron emission tomography (PET) employing several different radioisotopes has been used to interrogate brain function and metabolism in GBA-associated parkinsonism. [¹¹C]-CFT PET has demonstrated decreased uptake suggestive of presynaptic dopaminergic dysfunction in GBA heterozygotes and homozygotes with parkinsonism,^{54, 55} but normal uptake in asymptomatic GBA carriers⁵⁴. F-fluorodopa PET, which evaluates presynaptic dopamine terminals, has demonstrated reduced f-dopa uptake in the striatum of GD1 patients^{4, 56} and GBA-PD heterozygotes⁵², similar to IPD. Fluorodeoxyglucose (FDG) PET has shown hypermetabolism in the lentiform nuclei in GD1-PD patients, similar to IPD⁴. FDG-PET has also demonstrated cortical hypometabolism to varying degrees in the parietal, parieto-occipital and temporal lobes in both GD1-PD patients⁴ and GBA-PD patients⁵², correlating with the cognitive impairments seen in these subjects. One recent study⁵⁷ demonstrated that GD1-PD patients and IPD patients had comparably diminished striatal f-dopa uptake on F-fluorodopa PET, but that GD1-PD patients also had diminished resting regional blood flow in the parieto-occipital and precuneal cortices as visualized by H₂ ¹⁵O PET. This latter finding is similar to that seen in DLB, and underscores the cortical involvement in GD1 patients with PD⁵⁷.

Risk of PD associated with GBA mutations, and the relation between mutation type and risk and severity of PD

On the expanding list of hundreds of GBA mutations and polymorphisms, the N370S and L444P mutations are among the most common in those of Ashkenazi Jewish descent², and are most frequently studied across all ethnic groups. GBA mutations range from “mild” mutations such as N370S, which results in slightly diminished β -glucocerebrosidase activity,

to mutations causing a severely dysfunctional enzyme, or null mutations resulting in no protein production at all². The severity of mutation may modify the risk of developing parkinsonism, with mild mutations such as N370S and R496H conferring about twice the risk of disease compared to non-carriers, but more severe mutations (including 84GG, IVS2 + 1, V394L, D409H, L444P, RecTL) conferring over 13 times the risk¹⁰. Mutation type may affect age of onset, with patients carrying more severe GBA mutations having an average age of onset 2 years earlier than those with mild mutations¹⁰. Some researchers have also found that, among carriers of severe mutations, those with null or complex mutations had earlier age of onset than those with missense mutations⁷, and had increased risk of developing parkinsonism⁵⁸. It has also been suggested that there is a dose-effect related to carrying two mutant alleles, as GBA homozygotes or compound heterozygotes have an average age of onset 9.5 years younger than non-carriers¹⁰, and GD1 patients with parkinsonism frequently develop motor symptom onset before age 50^{3, 12, 14}. As in other complex genetic disorders with reduced penetrance, additional genetic factors and environmental modifiers are being sought. This discussion of genotype-phenotype correspondence and variable penetrance has significant genetic counseling implications among heterozygote carriers with PD, as the relative risk to offspring is very different depending on mutation.

Pathogenesis of GBA-PD, and its implications for treatment

The process by which GBA mutations promote neurodegeneration and parkinsonism is still being determined. An excellent recent review by Westbroek et al⁵⁹ summarizes much of the evidence linking GBA to PD pathogenesis, including data to support hypotheses both of a loss of β -glucocerebrosidase function, and of a gain-of-toxic-function by the abnormal enzyme, either of which could mediate α -synuclein accumulation. Most recently Mazulli et al have proposed a bi-directional loop whereby abnormal β -glucocerebrosidase promotes α -synuclein accumulation, and α -synuclein impairs β -glucocerebrosidase function, leading to subsequent neurodegeneration⁶⁰.

Genotype-phenotype correlations lend some support to the loss-of-function hypothesis, as null mutations of GBA, which result in the absence of a protein, significantly increase the risk of developing parkinsonism, and correlate with an earlier age of disease onset^{10, 58}. Multiple regions in GBA-PD brains, including substantia nigra, putamen, cerebellum and amygdala, have reduced levels of β -glucocerebrosidase protein and activity, unrelated to cell loss from neurodegeneration⁶¹. Brains of IPD subjects without GBA mutations also demonstrate reduced enzyme levels and activity in the substantia nigra and cerebellum (though to a lesser degree than in GBA-PD subjects)⁶¹, and it has been posited that there is a downstream role of β -glucocerebrosidase in non-GBA PD as well, likely due to accumulation of α -synuclein, and possibly due to oxidative stress and mitochondrial dysfunction. This has furthered theories that lysosomal enzyme dysfunction in general contributes to IPD pathogenesis, as there are reduced levels of multiple lysosomal enzymes in the cerebrospinal fluid of IPD subjects, including not only β -glucocerebrosidase, but also α -mannosidase, β -mannosidase and β -hexosaminidase⁶².

Multiple emerging lines of evidence point to an important relationship between β -glucocerebrosidase and α -synuclein. Mutant β -glucocerebrosidase and α -synuclein interact with each other at lysosomal pH⁶³; and in cell models mutant β -glucocerebrosidase promotes the accumulation of α -synuclein⁶⁴. β -glucocerebrosidase is present, along with α -synuclein, in an average of 75% of the Lewy bodies in the brains of GBA-PD subjects, but is a component of <10% of Lewy bodies in non-carrier PD subjects⁶⁵. In the feedback loop model, glucocerebroside, a substrate of β -glucocerebrosidase, may promote stabilization of α -synuclein into oligomers similar to those found in Lewy bodies, and mutations in β -

glucocerebrosidase correspondingly lead to α -synuclein accumulation; at the same time, α -synuclein impairs β -glucocerebrosidase function within lysosomes, both in PD cells and in normal cells, promoting further accumulation of glucocerebroside⁶⁰.

Significant evidence also supports a gain-of-toxic function by mutant β -glucocerebrosidase as an explanation for GBA-associated PD, although this is hard to reconcile with the fact that null mutations are also associated with PD. Mutant β -glucocerebrosidase may disrupt a neuron's machinery for eliminating abnormally-folded proteins, not only through lysosomal dysfunction, but also by impairing the endoplasmic reticulum-associated degradation (ERAD) of proteins. Parkin, a ubiquitin E3 ligase involved in ERAD, aggregates with mutant β -glucocerebrosidase, and stabilizes it rather than mediating its degradation⁶⁶. By aggregating with parkin, mutant β -glucocerebrosidase may impair parkin's activity, resulting in an accumulation of its misfolded protein substrates, which are cytotoxic⁶⁶.

Magnetic resonance spectroscopy (MRS)⁶⁷ has revealed some unique aspects of GBA-associated PD pathophysiology. It has demonstrated normal levels of high-energy phosphates⁶⁷, supporting the idea that mitochondrial dysfunction is not a major contributor to GBA-associated PD⁵⁹. MRS has also demonstrated elevated levels of certain unusual membrane degradation products in GBA-PD⁶⁷, which may reflect altered brain lipid metabolism. The finding that GBA-PD subjects have lower cerebrospinal fluid concentrations of total fatty acids and numerous specific fatty acids compared to IPD⁶⁸ also implicates abnormal brain lipid metabolism in the pathogenesis of GBA-associated PD.

Treatment of GBA-associated PD: PD-focused therapies

To date, no large-scale studies have specifically addressed the relative benefits and risks of different treatments for GBA-related PD compared to IPD. Thus, treatment of GBA-related PD currently follows the same principles as treatment of IPD, addressing motor, cognitive and neuropsychiatric manifestations as needed.

Early reports of GD1-associated parkinsonism described a levodopa-resistant disease^{12, 13}, but others have reported more typical-appearing, levodopa-responsive patients¹⁴. One large study of mutant GBA heterozygotes with PD discovered that about 90% of them had a favorable, enduring response to levodopa; the remainder ranged from initially-responsive with subsequently diminished benefit, to completely unresponsive⁵. It should also be noted that another large study found a slightly but significantly greater burden of levodopa-induced dyskinesias among GBA-PD patients (62%) compared to IPD patients (50%), independent of levodopa dose and duration of treatment or disease⁷.

While neuropsychiatric and cognitive disturbances significantly burden GBA-PD patients, little is known about whether such disturbances require different treatment in GBA-PD patients compared to IPD patients. That said, in a retrospective investigation of neuropsychiatric comorbidities and their treatment in GBA-PD and non-carriers, Barrett and colleagues found that 41% of GBA carriers were treated with an acetylcholinesterase inhibitor, compared to 15% of non-carriers; the rate of antipsychotic use was not significantly different⁵⁰.

There are also limited data to guide decisions about surgical management of GBA-associated PD, with most of our understanding coming from isolated case descriptions. Pallidotomy may⁶⁹ or may not¹² be beneficial, while some patients have improved with bilateral subthalamic nucleus deep brain stimulation (DBS)⁷. Whether GBA-associated PD requires a particular surgical approach should be the subject of more systematic investigation.

Treatment of GBA-associated PD: GD-focused therapies

Enzyme replacement therapy revolutionized the treatment of Gaucher disease type 1 patients in the 1990s, significantly reducing morbidity from the bone, blood and visceral manifestations of the disease. Early reports of GD1 patients with parkinsonism were quick to note that neurological symptoms did not improve with enzyme replacement¹²⁻¹⁴. Another case report later showed that miglustat, which treats GD1 by lowering elevated substrates of glucocerebrosidase, was tolerated by a patient with GD1 and parkinsonism⁷⁰, although the suggestion that miglustat might have stabilized his neurological condition caused some contention⁷¹, as miglustat does not readily cross the blood-brain barrier. Recently, investigation in mouse models of GD1-PD found that viral-vector-mediated replacement of normal GBA genes in the CNS resulted in expression of normal β -glucocerebrosidase in brain tissue, improvement in memory function when virus was delivered to the hippocampus, and slowing of the rate of α -synuclein accumulation compared to mice administered a control virus⁷². Furthermore, administration of normal GBA to mice with wild-type GBA alleles but excessive α -synuclein expression enhanced β -glucocerebrosidase activity, and led to a reduction in soluble α -synuclein (with a trend toward reduction in membrane-bound α -synuclein, and no change in insoluble α -synuclein)⁷². These findings suggest the intriguing possibility that targeted GBA enzyme replacement in the CNS could slow, stabilize or reverse some of the neurological manifestations in GBA-PD. Furthermore, because β -glucocerebrosidase activity has been shown to be decreased in the substantia nigra of IPD brains without GBA mutations⁶¹, some have conjectured that therapies modulating β -glucocerebrosidase might impact on IPD as well^{72, 73}.

Implications for genetic counseling

The implications of the GBA/PD connection remain ambiguous for families carrying GBA mutations. While most patients with GD1 never develop parkinsonism⁵⁹, mutant GBA is considered a susceptibility gene that increases the risk of developing PD, and GBA mutations are highly prevalent among PD patients. As noted, GBA mutations have a heterogeneous effect on PD risk, with more severe mutations associated with a higher rate of disease than milder ones. Under an autosomal dominant model, penetrance has been estimated to be 7.6% at 50 years, 13.7% at 60 years, 21.4% at 70 years, and 29.7% at 80 years⁷⁴, although it may be inaccurate to consider GBA-associated PD as autosomal dominant⁷⁵ (see figure 1). While knowledge of gene status does not currently impact management of heterozygotes, if homozygotes or compound heterozygotes are identified, they should be referred for evaluation of the bone and other organ manifestations of GD.

Conclusion

The observation that homozygotes and heterozygotes for GBA mutations are at increased risk for developing parkinsonism and IPD has led to an explosion of research into the natural history and pathogenesis of GBA-related PD. This has prompted new approaches to understanding IPD more broadly, and to deciphering the underlying molecular biology of GBA-related PD, with the ultimate goal of optimizing treatment for this subgroup of IPD patients. Future work will need to determine whether GBA-PD patients benefit from different therapies than IPD patients, and to develop treatments that might target the unique pathophysiology of this PD variant. In the end, genetic testing may one day be able to identify patients who would benefit from specific, personalized treatments. Further, discoveries made through investigations into GBA-related PD may ultimately lead to enhanced treatment for all patients with Parkinson disease.

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- 6**. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. *N Engl J Med.* 2009; 361:1651–1661. [PubMed: 19846850] [This study demonstrated a clear association between GBA mutation carriage and Parkinson disease, in a large, heterogeneous, international cohort, which included 5691 subjects with Parkinson disease and 4898 healthy controls. A portion of the patients were Ashkenazi Jewish, in whom GBA mutations had previously been found to be associated with PD (see [21]). The initial mutation screening evaluated only the L444P and N370S mutations, which are the most commonly-found mutations in the Ashkenazi population. Among the Ashkenazi subjects, 15% of PD patients had GBA mutations, compared to 3% of controls; among non-Ashkenazi subjects, 3% of PD patients had mutations, compared to 1% of controls. Interestingly and importantly, however, the authors found that limiting to those mutations most common in the Ashkenazi population missed many mutations in non-Ashkenazi subjects: they extended analysis of GBA alleles to include whole-gene sequencing in 1883 non-Ashkenazi patients (and 1611 non-Ashkenazi controls), and found that 7% of patients had GBA mutations. The authors ultimately established an overall odds ratio of GBA carriage in PD patients versus controls of 5.43, reinforcing the notion that GBA mutation carriage is associated with Parkinson disease in many populations, not just the Ashkenazi population. Also of interest, the authors found some differences in Parkinson disease characteristics among GBA carriers and non-carriers, including earlier onset and slightly greater propensity toward atypical features among GBA carriers.]
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in their cohort of European patients. These results robustly reinforce the work of other authors in defining GBA as a potential genetic risk factor for PD.]

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found that, among Parkinson disease patients, 31.3% (95% CI, 22.2–40.4%) were carriers for one or two mutant GBA alleles, as opposed to a carriage rate of 6.2% among controls. Idiopathic Parkinson disease patients had a much greater likelihood of carrying GBA mutations compared to Alzheimer disease patients (odds ratio [OR] 10.8) and to controls (OR 7.0).]

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- 74*. Anheim M, Elbaz A, Lesage S, et al. Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. *Neurology*. 2012; 78:417–420. [PubMed: 22282650] [While earlier epidemiological studies established GBA carriage as a risk factor for Parkinson disease, the risk of developing Parkinson disease for an individual carrier has remained relatively undefined; thus, genetic counseling for family members of GBA carriers with PD has remained challenging. In this study, the authors reviewed the pedigrees of 525 probands with familial Parkinson disease, and screened a large number of family members, including those with and those without Parkinson disease, for GBA mutations. Using this data, and employing a model that assumes GBA is an autosomal dominant PD gene with incomplete penetrance, the authors calculated an age-related penetrance of PD in GBA carriers as 7.6% at age 50, 13.7% at age 60, 21.4% at age 70, and 29.7% at age 80. While some concerns have been raised about the study's methodology and assumptions (see [75]), this study provides an important starting point for gathering information that will guide genetic testing and counseling in families with Parkinson disease related to GBA mutations.]
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Figure 1.

The complex genetics of GBA-related Parkinson disease (PD). Most PD-related genes have fairly clear autosomal dominant (LRRK2) or autosomal recessive (ATP13A2, DJ1) inheritance. Certain genes (Parkin, PINK1) are largely autosomal recessive, although disease may be present in the heterozygous state. GBA is even more complex genetic: “mild” mutations could be considered risk factors for PD, or else autosomal dominant PD genes with a low penetrance; more “severe” mutations could be considered either stronger risk factors for PD, or autosomal dominant PD genes with a higher penetrance; and heterozygosity for two GBA mutations results in Gaucher disease (GD), type 1 of which carries an increased risk of developing PD. The relationship of GBA mutations to PD thus confounds the classical paradigm of monogenic disorders.

Table 1

Idiopathic Parkinson disease (IPD) versus GBA-related Parkinson disease. Whether or not GBA-related PD presents a truly unique phenotype is the subject of debate. Most of the time, patients with PD due to GBA mutations are clinically indistinguishable from IPD patients; however, in large cohorts, patients with GBA-related PD as a group do seem to differ from IPD patients as a group. The epidemiological and individual clinical relevance of these differences, in terms of prognosis, management, and treatment outcomes, remains to be determined.

Feature	IPD	GD1-PD	GBA-PD Severe mutations	GBA-PD Mild mutations
Clinical Findings				
Average age of onset	Late 50s-early 60s	Possibly younger than IPD & GBA-PD, but not well defined.	Possibly younger than IPD & GBA-PD w/mild mutations (mean 55.7 years [8])	Possibly younger than IPD (mean 57.9 years [8])
Levodopa response	++	+/-	++/-	++/-
Dyskinesias	variable	?	Possibly higher than IPD	Possibly higher than IPD
Prominent early cognitive impairment	-	+/-	+/-	+/-
Psychosis	+ < -	+/-	+/-	+/-
Depression	+/-	++/-	++/-	++/-
Olfactory dysfunction	+	+	+	+
Pathology				
Loss of pigmented cells in SNc	+	+	+	+
SN Lewy bodies	+	+	+	+
Cortical Lewy bodies	+/-	++/-	++/-	++/-
Imaging				
SNc hyperchogenicity on TCS	+	+	+	+
Midline raphe hypoechogenicity on TCS	+/-	++/-	++/-	++/-
Presynaptic DA dysfunction on PET	+	+	+	+

Key to abbreviations: IPD = idiopathic Parkinson disease; GD1 = Gaucher disease type 1; SN = substantia nigra, pars compacta; TCS = transcranial sonography; DA = dopamine; PET = positron emission tomography.