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The Role of Glucocerebrosidase Mutations in Parkinson Disease and Lewy Body Disorders

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Abstract

Mutations in the gene encoding glucocerebrosidase *(GBA)*, the enzyme deficient in the lysosomal storage disorder Gaucher disease, are associated with the development of Parkinson disease and other Lewy body disorders. In fact, *GBA* variants are currently the most common genetic risk factor associated with parkinsonism, and identified subjects with Parkinson disease are more than five times more likely to carry mutations in *GBA*. The mechanisms underlying this association are not known, but proposed theories include enhanced protein aggregation, alterations in lipid levels, and autophagy-lysosomal dysfunction promoting the retention of undegraded proteins. We review the genetic studies linking *GBA* to parkinsonism, as well as several of the mechanisms postulated to explain the association of *GBA* mutations and the synucleinopathies, which demonstrate how studies of a rare mendelian disease may provide insights into our understanding of a common complex disorder.

Keywords

Parkinson disease; Gaucher disease; Alpha synuclein; Glucoceerebrosidase; Lew body disorders

Introduction

Of the many genes now associated with parkinsonism, mutations in the gene encoding for glucocerebrosidase (*GBA*) are one of the most frequent genetic determinants known in Parkinson disease (PD). The surprising discovery of a link between a rare Mendelian disorder, Gaucher disease (GD), and the common complex disorders PD and Lewy body dementia (LBD) provides new opportunities to evaluate different pathways and mechanisms relevant to the pathogenesis of both disorders.

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Glucocerebrosidase is a lysosomal enzyme that catalyzes the hydrolysis of glucocerebroside, a membrane glycolipid, to ceramide and glucose [1]. The gene for glucocerebrosidase (*GBA*, Online Mendelian Inheritance in Man [OMIM] #606463) was mapped to 1q21-22, cloned and sequenced more than two decades ago [2–4]. It is located in a very gene-rich area, where seven genes and two pseudogenes are found within 85 kb of sequence [5]. The *GBA* gene encompasses 7.6 kb of sequence and includes 11 exons and ten introns [3]. The glucocerebrosidase pseudogene (*GBAP*) is a highly homologous 5.7 kb sequence located 16 kb downstream, with the same organization of exons and introns as *GBA* [3, 6].

Mutations in *GBA* result in defective glucocerebrosidase, the enzyme implicated in the most common lipidosis, GD (type 1, OMIM#230800; type 2, OMIM#230900; type 3, OMIM#2301000). First described in 1882, GD presents with hepatosplenomegaly, anemia, thrombocytopenia, bone involvement, and neurologic symptoms (types 2 and 3) [7]. Mutations in *GBA* include point mutations, insertions, deletions, frameshift changes, splice site alterations, and recombinant alleles reported in GD patients of different ethnicities [8•]. Patients with identical *GBA* genotypes may exhibit considerable clinical heterogeneity. To date, there are approximately 300 mutations and polymorphisms in the *GBA* gene that have been identified in patients with varying presentations of GD [8•]. Consequently, it is still unclear how identical mutations can present such vast clinical variability [9, 10].

Among the many phenotypes associated with GD are patients presenting with parkinsonian symptoms. During past decades, several case reports and case studies describing such patients appeared in the literature [11–13]. Later, it was noted that some family members of patients with GD who carry *GBA* mutations had an increased susceptibility for developing PD [14, 15]. LBD also was reported to occur with increased frequency in GD patients and carriers [16]. In recent years, multiple independent studies from around the world have supported the original work identifying an association between *GBA* mutations and development of Lewy body disorders.

Studies in Patients with Gaucher Disease and Parkinsonism

In one of the first attempts to explore *GBA*-associated parkinsonism, different molecular approaches were used to evaluate a 48-year-old patient presenting with GD and atypical parkinsonism, including direct sequencing of *GBA*; a nearby gene, metaxin 1; and other known Parkinson genes (α-synuclein and parkin) using multiple techniques [17]. Gene sequencing and Southern blotting were used to evaluate the *GBA* locus and demonstrated that the patient had genotype L444P/D409H and also carried a duplication encompassing the *GBA* pseudogene and metaxin 1. Northern and Western blotting performed to assess *GBA* expression and protein levels revealed low expression and trace levels of protein. The authors then assembled a series of 17 patients with GD who developed parkinsonism [18]. Molecular analysis of these cases revealed 12 different *GBA* genotypes, although N370S was the most frequent *GBA* mutation found. No mutations were identified in the exonic regions of parkin and α-synuclein genes.

A larger study of 57 subjects was instrumental in establishing the association between the two disorders. The study searched for *GBA* mutations in brain samples from patients diagnosed with PD. Based on sequencing analyses, *GBA* alterations were detected in 12 samples (21%), including those from eight individuals with mutations (N370S, L444P, K198T, R329C) and four with alterations (T369M, E326K) [19] that occur with similar frequency in patients and controls and are considered *GBA* polymorphisms [20]. A group from northern Israel then explored the association between *GBA* mutations and PD by screening 99 Ashkenazi patients with idiopathic PD and 1,543 healthy Ashkenazi Jews for six *GBA* mutations (N370S, L444P, c.84dupG, IVS+1A>G, V394L, and R496H) commonly

found among Ashkenazi Jews. The researchers identified these mutations in 31.3% of patients with PD versus 6.2% of healthy controls ($P<0.001$) [21].

Subsequently, various cohorts of patients with PD have been screened for common *GBA* mutations (most often N370S and L444P) or by sequencing the entire *GBA* gene [21–28, 29•, 30, 31•, 32, 33, 34•, 35, 36••]. These studies reported a higher frequency of *GBA* mutations among both Ashkenazi Jewish and non-Jewish populations with PD than in matched controls. Among different research centers, the frequency of heterozygous *GBA* mutations varied between 10.7% and 31.3% among Ashkenazi Jewish cases with PD and between 2.3% and 9.4% in non-Ashkenazi Jewish patients (Table 1). Some studies reported a lower frequency of *GBA* mutations [25], whereas others had statistically insignificant results [23, 28]. This discrepancy may be attributed to the specific mutations screened for in the respective studies, because it is now known that the mutation frequency differs greatly among different ethnic groups [37]. For example, among Ashkenazi Jews, the carrier frequency for *GBA* mutations is between 1 in 14 and 1 in 18, and the N370S variant accounts for 70% of the mutant alleles [1]. On the other hand, *GBA* mutations are found in less than 1% of the population in other ethnic groups, in which a greater number of different mutations are found. Consequently, screening for the *GBA* mutations common in Ashkenazi Jews is not a reliable strategy for other ethnic cohorts. Moreover, the N370S mutation may not be present in the Asian population, as it has not been identified in patients with Gaucher disease of East Asian ancestry [34•, 38].

Most of the published studies specifically investigated sporadic PD. Recently, Nichols et al. [32] studied *GBA* alterations in familial PD. First, they screened all *GBA* exons in one proband from 96 selected families with cases of PD. Nine *GBA* alterations were found in 21 cases, including four novel alleles (21.8%). The selection of these patients was based on the LOD (logarithmic odds) scores for microsatellite markers close to the *GBA* locus. The authors then checked 1,325 familial PD cases from 566 families and 359 controls for the variations identified in the first 96 families, and detected 161 carriers (12.2%) in these patients versus 5.3% of controls. Although this study is important because it demonstrates the increased frequency of *GBA* mutations in familial PD cases, the authors also included subjects with E326K and T369M as mutation carriers. After removing subjects carrying these polymorphisms, the mutation rate for the remaining screened mutant alleles was 4.1% in cases versus 1.1% in controls, consistent with other studies screening for only a limited group of *GBA* mutations. However, in another recent study investigating familial Parkinson cases from Japan, *GBA* mutations were found in eight of 34 complex families and in five of 34 probands (14.7%), and all affected family members had concordant variants. This study showed *GBA* variants to be associated with familial PD cases as well as sporadic disease [34•].

Although these initial cohort studies suggested that *GBA* mutations are a risk factor for parkinsonism, there were deficiencies in study design because of the lack of appropriate controls, mixed ethnicity of samples, screening for only a limited number of *GBA* mutations, and inaccurate definitions of *GBA* mutant alleles. To address these issues, a large multicenter cohort was assembled including patients from 16 different research centers, totaling 5,691 patients with PD (780 Ashkenazi Jews) and 4,898 controls (387 Ashkenazi Jews) [36]. Among Ashkenazi Jews, N370S and L444P were detected in 15% of patients and 3% of controls, whereas in patients with PD from other ethnic groups, the combined frequency of one of these two mutations was 3%. When full *GBA* sequencing was performed, 7% of non-Ashkenazi Jewish patients with PD were found to be mutation carriers. Overall, the odds ratio for carrying a *GBA* mutation in subjects with PD was 5.43 (95% CI, 3.89–7.57), rendering mutations in this gene a common risk factor for PD (Fig. 1). However, it is unknown whether any specific *GBA* mutations have a higher degree of

association with development of PD, as the frequency of each mutated allele in different populations appeared to be a reflection of the carrier frequency in that specific population.

GBA Mutations in Other Lewy Body Disorders

Because of the diversity of PD phenotypes encountered in these studies, investigators expanded their studies to determine whether *GBA* mutations are associated with other Lewy body disorders. The synucleinopathies include PD, LBD (encompassing dementia with Lewy bodies, Lewy body variant Alzheimer disease, and multiple system atrophy [MSA]). They are characterized by the deposition of inclusion bodies consisting primarily of fibrillated α-synuclein in the brainstem or cortical (limbic or neocortical) regions, as previously described [39, 40].

Initially, Goker-Alpan et al. [16] examined all *GBA* exons in DNA from brain samples of 75 autopsy cases with pathologically confirmed Lewy body disorders (28 PD, 35 LBD, and 12 MSA) and found *GBA* mutations in 23% of 35 cases with LBD, 4% of cases with PD, and none with MSA. Subsequently, screening for just N370S and L444P, Mata et al. [41] detected *GBA* alterations in 2 (3.5%) of 57 patients with dementia with Lewy bodies (P=0.045) compared with control subjects (0.4%). Farrer et al. [42] reported mutations in *GBA* in 6% of 50 brain samples from subjects with pathologically confirmed diffuse LBD. In a fourth study, Clark et al. [43] sequenced *GBA* in brain samples from 187 cases, including 95 individuals with LBD, 60 patients with Alzheimer disease, and 35 pathologically normal controls. They detected *GBA* mutations in 28% of cases with LBD, 10% of cases with Alzheimer disease, and 3% of control cases (P<0.001). Although *GBA* mutations were not found exclusively in cases with Lewy bodies, they showed that *GBA* carriers are significantly more likely to have Lewy bodies as a pathologic finding. Whereas the first study by Goker-Alpan et al. [16] had only 12 cases of MSA, a recent study from the United Kingdom screened all *GBA* exons from 108 pathologically confirmed cases of MSA and 257 controls. As with the first study, the authors failed to show any significant difference between cases and controls (P=0.66) [44]. Moreover, in a study from Poland of 66 patients with MSA, screening for mutations L444P and N370S yielded no mutation carriers [45].

Histopathologic Findings in *GBA* Mutation Carriers

Analyses of postmortem brain tissue from patients with GD who developed parkinsonism demonstrated classic PD pathology as well as Lewy bodies in hippocampal regions CA2 through CA4, which are areas affected in GD [18, 46, 47]. Kono et al. [48] used positron emission tomography to investigate underlying dopaminergic dysfunction in parkinsonism associated with *GBA* mutations and demonstrated presynaptic dopaminergic dysfunction characteristic of patients with PD. Neumann et al. [31•] showed that in addition to classic PD pathology, in PD samples carrying *GBA* mutations, α-synuclein inclusions were detectable in cortical areas corresponding to Braak stages 5 to 6. These findings are similar to LBD, suggesting that *GBA* carriers have more advanced neuropathologic disease. This result is similar to the study by Clark et al. [43] reporting *GBA* as a marker for cortical Lewy body pathologic findings, independent of histopathologic findings typical of Alzheimer disease.

Clinical Findings in *GBA* Mutation Carriers

Parallel to studies focusing on the mutation analysis of patients with parkinsonism, several groups focused on the associated clinical manifestations in *GBA* mutation carriers, including age of onset, motor symptoms, cognitive deficits, and response to L-dopa treatment. Although the earliest studies in patients with GD and PD reported early onset and treatment-refractory parkinsonism with prevalent cognitive decline [11, 18], subsequent publications

show there is a broad spectrum of parkinsonian phenotypes among *GBA* mutation carriers, with variations in both age of onset and treatment response.

The first patients reported with GD and PD developed parkinsonian features in their 40s and 50s, an age earlier than that of most patients with sporadic Parkinson cases [14, 18]. In subsequent studies, the age of onset of motor impairment was reported to be 1.7–6 years earlier in *GBA* mutation carriers than in patients without *GBA* mutations [21, 25, 27, 28, 31•, 32, 33]. *GBA* mutations also have been associated with earlier-onset (<50 years) PD, in which the frequency of *GBA* mutations was found to be twice that of late-onset cases [27, 28, 32]. Even among cohorts in which PD developed before the age of 50 years, *GBA* mutation carriers had an earlier age of onset of clinical symptoms [27, 29•].

There also are conflicting reports with respect to the efficacy of L-dopa treatment in carriers of *GBA* mutations. While some reports described parkinsonian symptoms in patients with GD to be poorly responsive to L-dopa treatment [18], several others reported good or excellent response to treatment among *GBA* carriers [26, 28, 31•, 41, 49].

Overall, most studies could not detect any significant difference in clinical manifestations and disease progression between *GBA* carriers and controls applying the unified PD rating scale, Mini Mental State Examination, and Hoehn and Yahr clinical evaluation scale. Parkinsonism associated with *GBA* mutations appears to be phenotypically indistinguishable from sporadic PD. However, some studies found a higher frequency of cognitive decline [31•, 49], bradykinesia [50], and olfactory dysfunction [49] and a lower frequency of rigidity [27, 29•] to be associated with *GBA* mutations.

Generally it has been difficult to ascertain whether a correlation exists between the *GBA* genotype and the severity of parkinsonian manifestations. Although most studies reported N370S as the most common mutation among patients with PD, it has been suggested that more severe *GBA* mutations confer an increased risk of developing parkinsonism [29•]. Mutations such as R120W and L444P also were reported to confer an increased risk in cases of familial PD [34].

Mechanisms for the Association of *GBA* Mutations and the Synucleinopathies

The relationship between *GBA* mutations and the pathogenesis of PD and other Lewy body disorders is not clear. Most autosomal recessively inherited forms of PD, as in the case of parkin, DJ-1, PINK1, and ATP13A2, are considered to be the result of loss-of-function mutations and present with early-onset disease. On the other hand, autosomal dominant forms of PD generally are attributed to gain-of-function mutations, as seen with the genes for α-synuclein and LRRK2 [51]. In parkinsonism associated with *GBA* mutations, both gain- and loss-of-function theories have been postulated. The neuropathologic findings in patients with both GD and PD, as well as *GBA* carriers, appear to be typical of other synucleinopathies, suggesting that glucocerebrosidase may contribute to aggregation of α-synuclein through enhanced protein aggregation or as a consequence of glucocerebrosidase deficiency.

Evidence Implicating Lipid Alterations as a Loss of *GBA* Function

Glucocerebrosidase degrades glucocerebroside to ceramide. It previously was postulated that alterations in ceramide metabolism are associated with Lewy body formation. By reviewing the literature, Bras et al. [52] identified a group of genes involved in ceramide metabolism associated with Lewy body pathology. The role of lipid homeostasis and lysosomal function is an expanding field of research. Conradi et al. [53] identified the accumulation of lipofuscin spheroids in the cortical regions of brains from patients with

neuropathic GD. These lipofuscin deposits, proposed to be ganglioside in origin, are undigested lysosomal material and indicate inefficient lysosomal degradation in GD.

It has been shown that α-synuclein binds to lipids in the plasma membrane and synaptic vesicles [54]. Although α-synuclein normally is an unstructured soluble protein, it can aggregate to form insoluble amyloid fibrils in pathologic conditions. The binding of lipids may be able to prevent the formation of the fibrillar forms of α-synuclein and the aggregation of this protein. It has been postulated that accumulation of polyunsaturated lipids that might accumulate as a result of deficient glucocerebrosidase activity may alter the sphingolipid composition of membranes and disrupt membrane binding of α-synuclein, thereby enhancing its accumulation in the cytoplasm [55–57].

Evidence of lysosomal dysfunction in another lysosomal lipid storage disease, Niemann-Pick type C, may represent an additional facet of the effect of unbalanced lipid homeostasis [56]. In this case, the dysregulation of lipid and cholesterol trafficking leads to a buildup in the lysosome and disrupts proteolysis, which may increase levels of undegraded proteins. In addition, Martinez et al. [57] showed that GM1 ganglioside lipid rafts interact with α-synuclein, and both Martinez et al. [57] and Sharon et al. [58] showed that fatty acids also may contribute to the oligomerization of α-synuclein.

To explore whether alterations in glucocerebrosidase affect α-synuclein metabolism, Manning-Boğ et al. [59] analyzed in vitro and in vivo effects of exposure to conduritol-β-epoxide (CBE), an established inhibitor of glucocerebrosidase, and demonstrated that exposure to CBE could increase α-synuclein accumulation as detected by increased immunoreactivity in cultured cells and in the substantia nigra of a mouse model. They also observed that exposure to CBE induced astrocyte activation and aggregation of α-synuclein within these cells. This might correspond to the previous observation of astrogliosis in postmortem brains of patients with GD who developed PD [47].

However, there are some shortcomings in the theory that *GBA* mutations in subjects with parkinsonism result in lipid alterations due to a loss of functional glucocerebrosidase activity. Ceramide levels in the cell are tightly regulated, and ceramide can be derived from many different degradative and synthetic pathways. The amount of enzymatic activity in Gaucher heterozygotes should be sufficient to prevent substrate accumulation, and there is no evidence that ceramide is deficient in patients with GD, even those severely affected.

Gain-of-Function Role for *GBA* Mutations

There are other observations that favor a gain-of-function role for *GBA* mutations. Recent studies demonstrated that some mutations in *GBA* result in a misfolded protein [60]. Misfolded glucocerebrosidase might contribute to parkinsonism by leading to lysosomal insufficiency, by impairing autophagic pathways necessary for preventing the synucleinopathies, or by overwhelming the ubiquitin–proteasome pathway.

Lysosomal Alteration and the Synucleinopathies—One potential mode of action is that glucocerebrosidase dysfunction might lead to lysosomal insufficiency, thereby reducing α-synuclein degradation. Lysosomes acquire proteins via fusion with vesicles or via specific receptor-mediated incorporation. de Duve [61] and Essner and Novikoff [62] canonically described the lysosome as the major cellular compartment for protein degradation. The lysosome is a specific target of investigation for studies of the synucleinopathies because multiple lines of evidence, including identification of genetic mutations and familial forms of PD, implicate impaired lysosomal function. Mutations in ATP13A2, a lysosomal-resident P-type ATPase, have been associated with the onset of parkinsonism with dementia [63], juvenile parkinsonism, and young-onset PD [64]. Cuervo et al. [65] originally demonstrated

that α-synuclein was degraded via chaperone-mediated autophagy, a lysosomal receptor-based pathway that degrades proteins containing the KFERQ peptide sequence (approximately 40% of all known proteins). Moreover, this pathway may be blocked by the A53T and A30P mutant variants of α-synuclein, as well as posttranslationally dopamine-modified variants of α-synuclein [66]. One speculation is that disturbances in the lysosome contribute to reduced α-synuclein degradation and consequently promote its aggregation.

Autophagic Dysfunction—An alternate theory is that *GBA* mutations may cause autophagic dysfunction, interfering with a process required for neuronal survival. Macroautophagy is a ubiquitous biochemical process common to all eukaryotic organisms. For autophagy to occur, induction via the mTOR or beclin 1/vps34 (class III PI3K) pathway initiates the production and involvement of various autophagy (Atg) proteins, including Atg5 and Atg7, and the posttranslational addition of a phosphatidylethanolamine to MAP-1A LC3 (also known as Atg8), which is a constituent and reliable biomarker of the double-membraned autophagic vacuole [67, 68]. The newly formed double-membraned structure envelops the cytoplasmic material, including protein aggregates and defective mitochondria, for delivery and fusion to acidic compartments such as lysosomes and late endosomes, where their contents ultimately are degraded.

In addition to the lysosome, the autophagic vacuole also has been determined to be a compartment requisite for α-synuclein clearance [69, 70] through the engulfment of the cytoplasmic or vesicular form of α-synuclein and its delivery to the lysosome for final degradation. Moreover, gene replacement of beclin 1 [71], which upregulates autophagy, ameliorates the deleterious effects of α-synuclein overexpression in animal models of PD and LBD. Reduced autophagy also can promote α-synuclein oligomerization [70]. Furthermore, disruption of autophagy, by ablation of the Atg5 or Atg7 genes, leads to the promotion of neuronal deposition of lipofuscin and polyubiquitinated aggregates [72, 73]. Finally, disruption of the autophagic pathway can reduce lipid metabolism, as Singh et al. [74] reported that lipids are transported to the lysosome via autophagy for degradation.

To complicate matters, ceramides are known inducers of autophagy [75], although their effect in GD or in *GBA* mutation carriers has not been characterized. Although these degradative pathways are intricately linked, it would appear that either mutated glucocerebrosidase or accumulated glucocerebroside may disrupt cellular pathways necessary for autophagic–lysosomal degradation. Moreover, as these pathways have significant crosstalk, it is conceivable that disturbances in one metabolic system, such as glucocerebrosidase function, would lead to proteolytic failure, ultimately resulting in α-synuclein aggregation, Lewy body formation, and neural degeneration.

Endoplasmic Reticulum Stress and Interruptions to the Ubiquitin–Proteasome Pathway—Another theory is that mutant glucocerebrosidase might overwhelm the ubiquitin–proteasome pathway, causing a delay in the degradation of accumulated proteins, including α-synuclein [76]. The proteasomal pathway degrades mutant glucocerebrosidase, and it has been shown that some mutant variants are not trafficked from the endoplasmic reticulum to the lysosome, where they attain their mature functional conformation, but rather are transported to the proteasome for degradation. Ron and Horowitz [77] showed that glucocerebrosidase undergoes ubiquitination and is degraded. This degradative process involves the heat shock protein chaperones and, consequently, is sensitive to alterations in levels of molecular chaperones. The same authors proposed that one deleterious mechanism of mutant *GBA* is that the protein undergoes parkin-mediated ubiquitination, creating an imbalance in protein degradation resulting in secondary toxicity [78].

One observation that conflicts with a gain-of-function mechanism relates to the spectrum of *GBA* mutations encountered in subjects with PD. Among the many different mutations encountered are c.84dupG, IVS2+1G>A, and recombinant alleles that would be considered null alleles. These mutations, albeit rare, make it hard to support a gain-of-function mechanism when no protein is being made. However, the very truncated forms of the mutant protein still might induce endoplasmic reticulum stress.

Conclusions

The association of glucocerebrosidase with parkinsonism was discovered not through genomic techniques, but rather through careful clinical observation and investigations. This unanticipated finding has opened new avenues for research on the synucleinopathies. Although the full pathogenesis of these disorders remains elusive, probing the contribution of mutations in *GBA* to the disease process very likely will prove fruitful, as this finding suggests that glucocerebrosidase and α-synuclein are implicated in a common cellular pathway. Whether the route is related to protein accumulation or to lipid dysregulation, the metabolic pathways, protein structure, protein interactions, and other properties relevant to this enzyme merit close evaluation. This story also illustrates how studies of rare disorders can provide insights into mechanisms and pathways relevant to common diseases.

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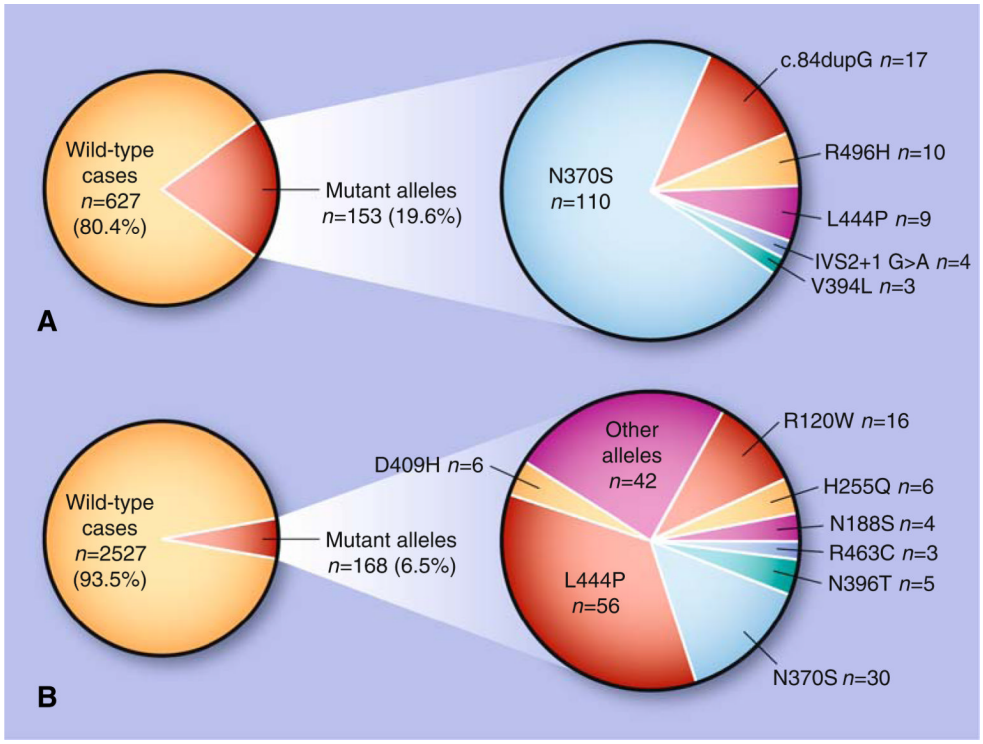

Fig. 1.

Frequency of *GBA* mutation carriers among patients with Parkinson disease and the distribution of different mutations in Ashkenazi Jews and non-Ashkenazi ethnic populations. **A** Twenty percent of Ashkenazi Jewish patients were found to carry a *GBA* mutation. **B** Among non-Ashkenazi Jewish patients for whom full sequencing was performed, 6.5% carried *GBA* mutations (from a meta-analysis by Sidransky et al. [36••]). The data in *panel B* are summarized based on whole *GBA* sequencing in three studies (Sidransky et al., 2009 [36••]; Neumann et al., 2009 [31•]; and Kalinderi et al., 2009 [33]). “Other alleles” include K(-27)R, K7E, R32H, R39H, R44C, R131C, R131S, D140H, R163Q, R163X, G193E, G193W, K198T, F213I, F216Y, R239C, R257Q, R262H, L268L, S271G, T323I, E326K, R329C, L336P, G344S, N370K, L371I, D380N, D380A, D443N, V460M, T482K, R496C, Q497R, c.1263-1317 del55bp, RecA456P, and Rec*Nci*I

Table 1

Frequency of *GBA* mutation carriers in individual Parkinson cohorts

Study	Population	Screened mutations	Sample size, *n*		Carrier frequency, %		*P* value	Most common variant(s)
			Cases	Controls	Cases	Controls		
Lwin et al. 2004 [19]	Mixed	Whole *GBA* scanning	57	–	21	–	–	N370S
Aharon-Peretz et al. 2004 [21]	Ashkenazi Jews	N370S, L444P, c.84dupG, IVS2 +1A>G, V394L, R496H	99	1543	31.3	6.2	<0.0001	N370S
Clark et al. 2005 [79]	Ashkenazi Jews	N370S	160	92	10.7	4.3	0.2	N370S
Sato et al. 2005 [22]	Caucasians (Canadian origin)	N370S, L444P, IVS2+1A>G, K198T, R329C, c.84dupG, Rec*Nci*I	88	122	5.68	0.8	0.48	Rec*Nci*I
Toft et al. 2006 [23]	Norwegian	N370S, L444P	311	474	2.3	1.7	0.58	N370S
Eblan et al. 2006 [24]	Mixed (no Jewish)	Whole *GBA* scanning	33	31	12	3.2	–	Rec*Nci*I, L444P
Tan et al. 2007 [25]	Chinese	L444P, N370S	331	347	2.4	0	0.06	L444P
Ziegler et al. 2007 [26]	Chinese	Whole *GBA* scanning	92	92	4.3	1.1	–	L444P
Wu et al. 2007 [28]	Taiwanese	L444P, Rec*Nci*I, R120W	518	339	3.1	1.2	0.07	L444P, Rec*Nci*I
Clark et al. 2007 [27]	Mixed (64% Jewish)	Whole *GBA* scanning	278 (178)	179	13.7	4.5	–	N370S, c.84dupG
De Marco et al. 2008 [80]	Italian	N370S, L444P	395	483	2.8	0.2	0.0018	L444P
Spitz et al. 2008 [30]	Brazilian	N370S, L444P, G377S	65	267	3	0	0.037	L444P
Mata et al. 2008 [41]	Mixed	N370S, L444P	721	554	2.9	0.4	<0.001	N370S, L444P
Gan-Or et al. 2008 [29•]	Ashkenazi Jews	N370S, R496H, L444P, c.84dupG, IVS2+1, V394L, D409H, RecTL	420	333	17.9	4.2	<0.0001	N370S
Bras et al. 2009 [35]	Portuguese	Whole *GBA* scanning	230	430	6.1	0.7	–	N370S, N396T
Kalinderi et al. 2009 [33]	Greek	Whole *GBA* scanning	172	132	4.7	0.8	0.048	H255Q, L444P
Nichols et al. 2009 [32]	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. 2009 [31•]	British	Whole *GBA* scanning	790	257	4.18	1.17	0.01	L444P, N370S
Mitsui et al. 2009 [34•]	Japanese	Whole *GBA* scanning	534	544	9.4	0.037	6.9×10^{-14}	R120W, Rec*Nci*I