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The association between mutations in the lysosomal protein glucocerebrosidase and parkinsonism

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Abstract

A body of work has emerged over the past decade demonstrating a relationship between mutations in glucocerebrosidase (*GBA*), the gene implicated in Gaucher disease, and the development of parkinsonism. Several different lines of research support this relationship. First, patients with Gaucher disease who are homozygous for mutations in *GBA* have a higher than expected propensity to develop Parkinson disease (PD). Furthermore, carriers of *GBA* mutations, particularly family members of patients with Gaucher disease have displayed an increased rate of parkinsonism. Subsequently, investigators from centers around the world screened cohorts of patients with parkinsonism for *GBA* mutations and found that overall, subjects with Parkinson disease as well as other Lewy body disorders have at least a five-fold increase in the number of carriers of *GBA* mutations as compared to age matched controls. In addition, neuropathologic studies of subjects with parkinsonism carrying *GBA* mutations demonstrate Lewy bodies, depletion of neurons of the substantia nigra and involvement of hippocampal layers CA2–4. While the basis for this association has yet to be elucidated, evidence continues to support the role of *GBA* as a Parkinson risk factor across different centers, synucleinopathies and ethnicities. Further studies of the association between Gaucher disease and parkinsonism will stimulate new insights into the pathophysiology of the two disorders, and will prove crucial for both genetic counseling of patients and family members and the design of relevant therapeutic strategies for specific patients with parkinsonism.

Keywords

parkinsonism; synucleinopathies; Gaucher disease; glucocerebrosidase; risk factor

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Introduction

Astute observations of clinical patterns made over time can lead to recognizable but unanticipated connections between very different diseases. Through the detailed study of a simple Mendelian disorder, Gaucher disease (GD) (MIM 230800, 2230900 and 231000), a tangible relationship between mutations in glucocerebrosidase and parkinsonism has evolved. Extending from clinical evaluations of individual patients, through larger patient cohorts, research has recently demonstrated that this single gene disorder may provide insights into the etiology and pathology of a more common complex disease.

Gaucher disease is the inherited deficiency of the lysosomal enzyme glucocerebrosidase, and is the most common of the lipidoses. Characteristic appearing Gaucher cells are a hallmark finding in patients with GD, reflecting the storage of the lipid, glucocerebroside, within the lysosomes of macrophages. Three major classifications of Gaucher disease have been created to differentiate different patient phenotypes.¹ Type 3, or chronic neuronopathic GD, yields a varying degree of systemic involvement, but at least one associated neurological manifestation; patients with type 2, or acute neuronopathic disease, suffer from an aggressive form of the disease that leads to death perinatally or within the first few years of life. Type 1 GD, which is the most common form, by definition has no central nervous system involvement. Associated clinical manifestations in all types of GD include hepatosplenomegaly, anemia, thrombocytopenia, easy bleeding and bruisability, bony involvement and, in some cases, pulmonary involvement. However, the distinction between the different types is often blurred, and many Gaucher phenotypes evade classification.²

Gaucher disease is an autosomal recessively inherited disorder. It is pan-ethnic in occurrence, but is encountered more frequently among Ashkenazi Jews. Patients inherit mutations in both copies of the glucocerebrosidase gene (*GBA*). *GBA* is found on chromosome 1q21–22 and consists of 11 exons encoding for a 497 amino acid protein. A highly homologous pseudogene sequence is located in the same locus, 16 kb downstream, complicating mutation analysis in this region. To date, almost 300 mutations have been identified in patients with Gaucher disease including point mutations, insertions, deletions, frame-shift mutations, splice site mutations and recombinant alleles.³ Among Ashkenazi Jewish patients, screening for the presence of six mutations can identify more than 90% of mutant alleles.¹ However, in patients of other ethnicities, a wide spectrum of mutant alleles is encountered and gene sequencing is a more reliable means of mutation detection.³

Clinical Descriptions of Patients with both Gaucher Disease and Parkinson Disease

In past years, a small subgroup of patients with GD was found to have a propensity to develop parkinsonism during their adult life. Most of the patients have type I GD. Parkinson disease (PD) is a neurodegenerative disease that is common among adults throughout the world, affecting 1% of people over the age of 65. PD is extraordinarily complex in cause and capacity to be treated. The presenting manifestations include bradykinesia, tremor, rigidity, asymmetric manifestations and postural instability. The neuropathology includes a loss of dopamine neurons and the eventual depigmentation of the substantia nigra (SN).

The first indication of a relationship between GD and parkinsonism came in the form of scattered case reports in the medical literature.^{4–6} Each described a patient with Gaucher disease, or a family member who developed symptoms of parkinsonism. In our clinic, concern first arose about a possible association between the two diseases in the late 1990's when we evaluated and treated a woman with relatively mild Gaucher disease who developed a tremor at age 42, followed by rapid deterioration of her gait.⁶ A pallidotomy

performed at age 47 was not helpful, and motor and cognitive decline ensued despite enzyme replacement therapy for Gaucher disease. While the presence of these two disorders could have been unrelated, the previous case reports as well as scattered clinical descriptions from colleagues prompted a solicitation and evaluation of similar cases.

Within a few years, we collected seventeen male and female individuals from several ethnicities, described in a 2003 report.⁷ These subjects suffered from mild Gaucher manifestations with a mean age at diagnosis of 35 years. However, their parkinsonism presented relatively early, at a mean age of 48 years. Classic parkinsonian symptoms were described. Although four patients were treated with enzyme replacement therapy, Parkinson disease symptoms persisted. Additionally, several subjects described a family history of parkinsonism, even among family members without GD. Of note, while a variety of different genotypes were encountered among the 17 probands, mutation N370S, previously considered to be associated exclusively with non-neuronopathic GD, was the most common allele found.

More recently, subjects carrying *GBA* mutations were evaluated prospectively at the NIH Clinical Center with detailed neurological examinations.⁸ The findings of ten subjects (7 males, 3 females) with parkinsonism and *GBA* mutations were recently summarized. Mutations N370S, L444P, c.84dupG and recombinant alleles were all identified in patient DNA samples. The subject group had a mean age of disease onset of 49, disease duration was 7.8 years (1.2–16), and the mean Uniform Parkinson Disease Rating Scale (UPDRS III) motor score off therapy was 26.3. Cognitive changes were reported by half of the subjects, substantiated by formal neuropsychiatric testing. Six patients were diagnosed with Parkinson disease, three patients had Lewy body dementia, and one further patient in the series was diagnosed with a “Parkinson plus” syndrome. Atypical manifestations included electroencephalographic abnormalities, myoclonus and seizures. Olfactory dysfunction was the most common non-motor finding. Thus, it appears that glucocerebrosidase mutations are associated with a broad spectrum of synucleinopathies, including classic PD, and less common disorders such as LBD. This study is being expanded, and is utilizing different functional and imaging techniques to identify potential biomarkers for PD in this population, as well as a better phenotypic assessment of these subjects.

The next major finding was the discovery of an increased incidence of *GBA* mutations in cohorts with parkinsonism. One study screened DNA extracted from brain tissue of patients with Parkinson disease for mutations in the *GBA* gene.⁹ Mutations were found more frequently than expected. Of the 57 different DNA samples collected from five separate American brain banks, eight (14%) had confirmed mutant alleles; two of these mutant samples were *GBA* homozygotes, and six were heterozygotes. Five of the identified mutant alleles had the common N370S mutation, which is associated with non-neuronopathic GD. This study also included 44 age-matched controls without pathological evidence of PD, none of which carried mutations. The *GBA* mutations were found in DNA samples from patients with an earlier age of onset. DNA samples were also collected from brain bank samples in Britain, revealing that two (8%) of the 26 cases with PD carried *GBA* mutations.¹⁰

Other studies have screened cohorts of Parkinson patients for one or more specific *GBA* mutations. One such clinic-based study in Northern Israel screened 99 Ashkenazi patients with classic PD symptoms.¹¹ DNA samples were tested for several common glucocerebrosidase mutations. Strikingly, 31 (31.3%) patients screened carried a N370S or c.84insG mutation, representing a five-fold increase above the two control groups screened, 74 patients suffering from Alzheimer's disease (AD), and 1543 young Ashkenazi controls. The controls collected were less than ideal however, because of the lack of both selectivity and neurological evaluations in the control groups.

These findings have since been supported by studies of *GBA* mutations in other groups of patients with PD around the world. A study conducted by investigators at Columbia University screened 160 Ashkenazi Jewish probands with PD and 92 clinically evaluated control subjects of Jewish ancestry from a New York City clinic.¹² When each subject was screened for the N370S mutation, 17 probands (10.7%) carried the mutation while only 4.3% of the controls had a mutation. Later, the same group revisited the question with a larger sample, sequencing *GBA* in a cohort of 278 subjects with PD (178 Ashkenazi Jews) alongside 179 controls (85 Ashkenazi Jews) enrolled in the Genetic Epidemiology of Parkinson Disease (GEPD) study.¹³ They reported that 13.7% of patients with PD carried mutations in *GBA*, while only 4.5% of the controls were positive for mutations. *GBA* mutations were most frequent among patients with an age at onset below 50 years of age (22%). In this study, the age at onset was 1.7 years earlier among patients with *GBA* mutations, when controlling for age, sex, family history, and Jewish ancestry. A larger study in Ashkenazi Jews conducted by Gan-Or, *et al.* in Israel examined a cohort of 420 PD patients, 333 elderly controls, and 3805 young controls, all of whom were screened for eight common *GBA* mutations.¹⁴ The elderly and PD patients were also screened for the LRRK2 G2019S mutation, and while one-third of the patients screened carried this mutation, only four had both G2019S and a *GBA* mutation. In this study, *GBA* mutations were found in 17.95% of the PD patients, a significantly higher frequency than the 4.2% observed among elderly and 6.35% among young controls. Among the identified mutations were two early frame-shift mutations, which conferred a high odds ratio. Finally, this study again found that the age at onset of PD was lower among those carrying *GBA* mutations.

There have also been studies conducted in non-Jewish cohorts. A study from Toronto screened 88 unrelated Canadian PD subjects for seven different mutations in the *GBA* gene, including two very rare alleles.¹⁵ The subjects were selected because of either a family history of PD, or because of early onset of symptoms. The control group consisted of 122 clinically screened Canadians. Mutations were observed in 5.6% of patients diagnosed with PD, while only 0.8% of the controls carried a mutation.

Two further studies performed in South America gave similar results. One study using samples from Venezuela sequenced the entire *GBA* gene among 33 PD patients and 29 control subjects. Four (12%) unrelated PD patients carried *GBA* mutations, each with earlier onset disease.¹⁶ In a study from Brazil, 62 probands were investigated for *GBA* mutations. 17 Two (3.5%) were found to have common mutations while none were found among 267 age and sex-matched controls.

Another study initiated by Bras, *et al.* examined a cohort of Portuguese PD patients.¹⁸ A total of 230 patients were examined and compared to 430 controls. The PD sample group identified 14 heterozygotes for *GBA* mutations (N370S, N396T, D409H, and L444P), while the control group had three N370S. Additionally, two polymorphisms, E326K and T369M, previously described as non-pathogenic, were found among controls and patients. Two novel variants and one mutation of unknown significance were also identified. A 6.1% frequency of *GBA* mutations was observed among the PD patients, compared to a frequency of 0.7% among the controls. Since in this study, as well as others using non-Ashkenazi cohorts, the *GBA* mutations identified included many rare alleles, it appears to be necessary to sequence all patient samples in studies among non-Ashkenazi PD patients.

Several additional studies have screened for the presence or absence of two common *GBA* mutations, N370S and L444P in large Caucasian PD cohorts. Mata, *et al.* found the two mutations in 2.9% of 721 PD subjects from Seattle versus 0.4% of 554 controls.¹⁹ However, Toft, *et al.*, screening 318 probands from Norway found a mutation frequency of 2.3 %, which did not differ significantly from the 1.7% seen in 412 controls.²⁰ A group in Italy

reported the presence of one of these two mutations in 2.8% of patients and 0.2% of controls.²¹

Because it had been argued that ethnicity could have confounded our initial results, we focused on a specifically non-Jewish cohort of 184 Chinese patients from Taiwan with Parkinson disease, as well as 92 clinically screened and ethnically/age-matched controls using DNA plates from the NINDS Human Genetic Resource Center (Coriell).²² *GBA* sequencing demonstrated that mutations were present in 5.4% of the PD patients, while only in 1.1% of controls. Several mutant alleles were found including mutations L444P and D409H, as well as rare or novel mutations such as L174P, R131S, R163Q, S271G, and Q497R. These results demonstrated that the link between Gaucher and Parkinson diseases was independent of the ethnicity of the group studied. These results were also confirmed in two other Asian PD cohorts.^{23, 24}

A recent paper explored the frequency of *GBA* alterations in familial cases of PD.²⁵ In this study, 12.6% of familial PD patients screened were shown to have *GBA* alterations, while they were only seen in 5.3% of controls. However, when subjects carrying E326K and T369M were removed, the frequency of other *GBA* mutations was 4.1% in cases versus 1.1% in controls, which is similar to non-familial cohorts.

For the most part these studies have independently reached similar results demonstrating that *GBA* mutations are seen in patients with PD at a higher frequency than expected. Although it is premature to attempt to determine the risk of PD among *GBA* mutation carriers, even heterozygotes appear to be at increased risk. A large meta-analysis, pooling genotypic data from 16 different centers from around the world is in progress. This study will more definitively establish the Odds Ratios across different ethnicities and provide information that ultimately may be useful for genetic counseling.

Other Lewy Body Disorders

It has been observed that the neuropathologic spectrum associated with *GBA* mutations is actually quite broad. *GBA* was examined in 75 autopsy specimens with different synucleinopathies.²⁶ *GBA* mutations were identified in 23% of cases of Lewy body dementias (LBDs), including subjects with the pathological diagnoses of Lewy Body Variant Alzheimer disease (LBVAD) and dementia with Lewy bodies (DLB).²⁶ An additional 35 samples were recently sequenced and two heterozygotes and one homozygote were found.

Phenotypic Features of Heterozygotes

Reports that patients with heterozygous *GBA* mutations have a particularly severe parkinsonian phenotype have been contradicted by other reports that mutations are associated with a variety of symptoms. In Aharon-Peretz, *et al.*'s report of 40 PD subjects with a *GBA* mutation and 108 control PD subjects, a clear difference was not seen.²⁷ The spectrum of symptoms observed included variable degrees of rigidity, bradykinesia, hallucinations, and dementia. There is preliminary evidence that overall, mutation carriers have an earlier age at onset and more cognitive changes. The earlier age of onset has been confirmed in other studies. Nichols, *et al.* found that the average age at onset for Parkinson patients with *GBA* mutations was 6.4 years earlier than other patients.²⁵

One potential tool for identifying parkinsonism in GD patients may relate to smell. The results of olfactory testing suggest that smell tests may serve as an early biomarker of disease. While differing olfactory deficits occur in patients with synucleinopathies, a markedly decreased sense of smell remains highly characteristic of PD.²⁸ Although

olfactory dysfunction is a less prominent finding in PD resulting from other gene mutations, including alpha-synuclein²⁹ and *LRRK2*.³⁰ Preliminary evidence indicates that parkinsonian subjects with *GBA* mutations demonstrated well-defined deficits in smell.

Parkinson Disease Among Family Members of Gaucher Probands

The association of Parkinsonism and *GBA* heterozygotes has not been limited to molecular studies of PD patients, but has included family studies of patients with Gaucher disease as well. In a small pilot project carried out in the Gaucher clinics at the National Institutes of Health, carefully ascertained pedigrees were collected on all Gaucher probands, specifically inquiring regarding a family history of parkinsonism, tremor or dementia. This study found that ten of 40 families interviewed reported a family history of PD in obligate *GBA* mutation carriers.³¹ These were often parents or grandparents of GD probands.

One such example was the case of a seven-year-old boy with type 3 Gaucher disease. Multiple paternal relatives over several generations had symptoms of parkinsonism. Clinical examinations and DNA testing of both affected and unaffected family members revealed that heterozygosity for the L444P mutation in the *GBA* gene directly correlated with Parkinson disease. These results were consistent throughout the group of families that were investigated, providing increasing evidence that *GBA* mutations are a contributing factor to parkinsonism.

Halperin, *et al.* published a report citing an increased risk of parkinsonism among family members of patients with Gaucher disease. A total of 107 patients, 59.4% of whom were homozygous for the N370S mutation, were questioned about family members with PD.³² Within this group of subjects, ten (17.5%) reported having a family member with Parkinson disease. Of the 39 subjects who were heterozygous for a *GBA* mutation, five (12.8%) had a relative with Parkinson disease. Among the control group questioned, 12.3% reported having a family member with PD. Another study from Spain also noted an increased frequency of PD among relatives of Gaucher probands.³³

Neuropathologic Findings

Neuropathologic studies of samples from patients with Gaucher disease and parkinsonism have been somewhat limited. Among patients with type 2 and 3 Gaucher disease, periaxonal accumulation of Gaucher cells was the most common pathology observed.¹ In the basal ganglia, midbrain, pons and medulla, cerebellum, dentate nucleus and hypothalamus, significant neuronal loss with atrophic neurons occurred.³⁴⁻³⁵ In a recent neuropathological study including samples from subjects with all three types of GD, specific pathologic patterns of disease were identified. These were much more pronounced in patients suffering from types 2 and 3, and involved hippocampal CA2-4 regions and layer 4b of the cortex.

In the samples from subjects with both Gaucher and Parkinson diseases, Lewy bodies, depletion of SN neurons, SN gliosis, and gliosis of the hippocampal layers CA2-4 were observed.³⁶ Two patients had intraneuronal, synuclein-positive inclusions in the CA2-4 regions similar to the brainstem-type Lewy bodies, while others had a Lewy body distribution similarly to that seen in LBD.

Proposed Mechanisms for this Association

Parkinson disease is one of a number of diseases that display abnormal fibrilization and an accumulation of proteinaceous, insoluble alpha-synuclein in neurons and glia, indicating a shared cellular pathology for the handling and clearance of alpha-synuclein.³⁷ Other

neurodegenerative diseases that feature abnormal alpha-synuclein pathology include dementia with Lewy bodies (DLB), the Lewy body variant of Alzheimer disease (LBVAD), and rare conditions such as multiple system atrophy (MSA), and neurodegeneration with brain iron accumulation (NBAI-1).³⁸ While this protein has little or no detectable secondary structure in solution, and is considered to be natively unfolded, binding of alpha-synuclein to a number of ligands and proteins alters this native state and leads to partially folded conformations.³⁹ Studies have demonstrated that mutations in alpha-synuclein⁴⁰, as well as overexpression of the protein, result in aberrant aggregation of alpha-synuclein, which is associated with neuronal death. These aggregated insoluble polymers are proposed to be necessary prerequisites for Lewy body formation, but Lewy bodies also contain other proteins.⁴¹ The pathology associated with alpha-synuclein mutations may resemble DLB, and is extremely widespread. The pathology exhibited in *GBA* homozygotes, as well as heterozygotes, encompasses the spectrum of synucleinopathies, including DLB, suggesting that glucocerebrosidase may contribute to aggregation of alpha-synuclein through a gain-of-function mechanism whereby mutated glucocerebrosidase enhances the quantity of aggregates.

It has long been postulated that the ubiquitin-proteasome system (UPS) in PD patients is compromised.⁴² Cytotoxic proteins collected in Lewy bodies suggest that the aggregated polymers are caused by protein mishandling and result in proteolytic stress. Furthermore, rare familial PD cases are caused by alteration in genes, such as parkin that play a role in the UPS pathway.⁴² Since most mutations in glucocerebrosidase are missense mutations, they likely lead to an aberrantly folded protein which might , overwhelm the UPS, and prevent adequate degradation of accumulated proteins including alpha-synuclein, again supporting a gain of function mechanism.

Alpha-synuclein mutations result in the formation of oligomers, called protofibrils. While protofibrils remain soluble, they can form toxic annular structures that cause damage to membranes.⁴⁴ Wildtype alpha-synuclein, and perhaps other types of soluble forms of the protein such as protofibrils, are degraded via a lysosomal degradation pathway, chaperone mediated autophagy (CMA).⁴⁶ Using PC12 cells, it has been shown that the heat shock protein hsc70 is the chaperone molecule that binds with alpha-synuclein in the cytosol, and subsequently Lamp2a acts as a receptor to internalize the bound protein into the lysosome.⁴⁶ Mutant alpha-synuclein could stay bound to the chaperone and fail to become internalized by the lysosome, remaining bound to the Lamp2a receptor. Heterozygous mutations in glucocerebrosidase could possibly lead to lysosomal dysfunction or may interfere with receptor binding of alpha-synuclein at the lysosomal membrane, causing cellular toxicity.

Yet another theory about the relationship of glucocerebrosidase to synucleinopathies involves the helical binding of alpha-synuclein to lipid membranes.⁴⁷ This binding would prevent the formation of fibrillar protein structures. Some studies suggest that alpha-synuclein accumulation and toxicity is promoted by glucocerebrosidase. It has been demonstrated that alpha-synuclein does bind to brain-derived glycosphingolipids that contain glucocerebrosidase in their core.⁴⁸ Therefore, patients with Gaucher disease might potentially accumulate the substrates glucocerebrosidase and/or glucosylsphingosine, which may interfere with lipid binding of alpha synuclein. However, since *GBA* mutant carriers do have a functional amount of glucocerebrosidase, it is not clear that substrate concentrations would be altered in heterozygotes.

It has also been suggested that ceramide metabolism may play a role in the development of parkinsonism. A decrease in glucocerebrosidase resulting from either homozygous or heterozygous *GBA* mutations could result in decreased ceramide metabolism. In a recent

review, Bras, *et al.* summarize a number of genes involved in ceramide metabolism that, when mutated, result in Lewy body pathology.⁴⁹ However, ceramide levels are generally tightly regulated, and it is not clear whether a partial deficiency in glucocerebrosidase would impact ceramide metabolism significantly.

Screening and Treatment

Like many other neurodegenerative diseases, the treatment of Parkinson disease can be quite challenging. Currently, there is only symptomatic treatment, which has variable success among different synucleinopathies. Our incomplete understanding of the etiology and pathogenesis of these diseases has hindered further optimization of treatment options or early diagnostic strategies.

Currently, parkinsonism in patients with GD is treated with conventional therapies for PD. While several patients have received enzyme replacement therapy, there is no evidence that such treatment contributes to a slowing of the progression of Parkinson disease symptoms. Recombinant enzyme does not cross the blood-brain barrier, and therefore has not been shown to provide any benefit for the treatment of the neurological symptoms displayed in patients with type 2 and 3 GD. Furthermore, as increased numbers of heterozygotes for *GBA* mutations with PD are identified, it seems unlikely that providing supplemental enzyme would be a wise strategy. Since heterozygotes have ample functional enzyme, additional enzyme would certainly not be expected to have tangible benefit, and other modalities will need to be developed. Another strategy proposed for the treatment of GD disease is substrate reduction therapy with aminosugar derivatives like Miglustat. This therapeutic approach aims to reduce the amount of glucocerebroside by inhibiting its synthesis. However, since there is no solid evidence that substrate accumulation results in the parkinsonian manifestations seen, the potential use of these drugs is unlikely. Pharmacological chaperones are also being considered as a therapeutic strategy. Some *GBA* mutations are thought to result in protein misfolding.⁵⁰ If glucocerebrosidase misfolding or impaired trafficking contribute to the development of synucleinopathies in *GBA* mutation carriers, then it is conceivable that specific chemical chaperone therapies could be utilized to treat these patients.

Implications for Genetic Counseling

The results of these studies may eventually impact genetic counseling both for PD subjects found to carry *GBA* mutations, and for patients and families with Gaucher disease. As when dealing with any late-onset neurodegenerative disorder, great care must be taken to avert undue alarm. Patients must be carefully counseled regarding the concept of a risk factor. After extensive experience in treating patients with Gaucher disease world-wide, it is evident that only a small percentage develop parkinsonism.⁵¹ Likewise only a small proportion of carriers of *GBA* mutations ever develop parkinsonism, even in families where both diseases have occurred with some frequency. For now, it remains important that families be counseled to understand that a mutation in the *GBA* gene remains one of many potential risk factors contributing to a susceptibility to parkinsonism, and that currently there is no proven preemptive therapy for at risk individuals.

However, it is essential that clinicians be aware of the relationship between these two disorders to facilitate a better understanding of the etiology and implications of such a connection. With this in mind, clinicians should thoroughly inquire regarding a family history of dementia or tremor while performing evaluations of patients with GD. Furthermore, in Parkinson clinics, patients should be questioned about family members with GD.

Ultimately, if specific therapies are targeted toward *GBA* associated parkinsonism, this will have wide implications. Potentially, at-risk subjects could be screened for *GBA* mutations, and therapies be applied pre-symptomatically. This is one of the reasons why this association provides such an exciting avenue of study.

Conclusion

As further cases of *GBA* associated Parkinson disease are identified and studied, new insights will continue to evolve regarding the complex relationship between *GBA* and parkinsonism. For example, the role of mutant glucocerebrosidase in the aggregation of alpha-synuclein and the formation of Lewy bodies merits close attention. While mutant glucocerebrosidase clearly appears to be associated with an increased incidence of Lewy body disorders in carriers of mutant *GBA*, establishing the mechanism for this association will be crucial.

Currently, the frequency of *GBA* in cohorts with parkinsonism is increased around five-fold. However the risk of a heterozygote developing Parkinsonism cannot be easily calculated and this estimation will be critical for determining an individual's susceptibility. Furthermore, other possible modifiers that may affect a patient's risks of developing PD must be investigated. For example, other specific environmental or genetic factors may play a role. These conclusions can only be drawn, however, when large amounts of data have been assembled.

It has been established that enzyme replacement therapy for Gaucher disease does not serve as a viable treatment option for heterozygotes or homozygotes with PD. While L-dopa treatment can significantly improve the quality of life, once the mechanism for this association is better established more promising therapies must be identified and developed for PD patients with *GBA* mutations.

The association of mutant glucocerebrosidase with parkinsonism is a truly exciting new chapter in the study of this common complex disease. It is a great example of how clinical insights can drive genetic studies in ways not anticipated from large genetic screens. It also demonstrates how studies of rare genetic disorders can shed light on other seemingly unrelated fields of study.

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