Genetics inMedicine | BRIEF REPORT



# Age-specific Parkinson disease risk in *GBA* mutation carriers: information for genetic counseling

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**Purpose:** We sought to estimate age-specific risk of Parkinson disease in relatives of patients with Gaucher disease, who are obligate carriers of *GBA* mutations and who were not ascertained by family history of Parkinson disease.

**Methods:** A validated family history of Parkinson disease questionnaire was administered to 119 patients with Gaucher disease who were evaluated at the Mount Sinai School of Medicine from 2009 to 2012; the ages of their parents, siblings, and children, history of Parkinson disease, age at onset of Parkinson disease, and ethnic background were obtained. Kaplan–Meier survival curves were used to estimate age-specific Parkinson disease penetrance among parents of patients with Gaucher disease , who are obligatory *GBA* mutation carriers.

**Results:** Two participants with Gaucher disease were affected by Parkinson disease (5.4% of those who were 60 years or older). Of the 224 informative parents of patients with Gaucher disease, 11 had Parkinson disease (4.9%). Among the parents (obligatory carriers), cumulative risk of Parkinson disease by ages 65 and 85 was estimated to be 2.2% ±2.1% and 10.9% ±7.2%, respectively.

**Conclusion:** We provide useful age-specific estimates of Parkinson disease penetrance in patients with Gaucher disease and *GBA* heterozygous carriers for genetic counseling. Although *GBA* mutations may increase the risk for PD, the vast majority of patients with Gaucher disease and heterozygotes may not develop the disease. Further studies are needed to identify what modifies the risk of Parkinson disease in *GBA* mutation carriers.

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**Key Words:** family history; Gaucher disease; *GBA* mutations; glucocerebrosidase; Parkinson disease; risk

## INTRODUCTION

Gaucher disease (GD) is the most prevalent inherited lysosomal storage disease. GD results from biallelic mutations in the β-glucocerebrosidase gene (*GBA*) on chromosome 1q21 and causes deficient enzyme activity of acid β-glucosidase or glucocerebrosidase. Three main forms of GD exist; type 1 is most common. Phenotypic expression of type 1 GD can vary from asymptomatic individuals to those with systemic involvement including hepatosplenomegaly, thrombocytopenia, and bone disease. As many as 8.3% of Ashkenazi Jews (AJ) carry a mutation in *GBA*, and p.N409S (N370S) is the most common mutation in this population.[1,2] Up to 1% of non-Jews carry a mutation in the *GBA* gene.[3]

After Alzheimer disease, Parkinson disease (PD) is the second most common neurodegenerative disease. Although type 1 GD was originally defined as non-neuronopathic, in 1996, Neudorfer et al.[3] published a study describing six patients with type 1 GD and parkinsonism, suggesting a neurological involvement in a subset of type I GD. It is estimated that there is a 6- to 11-fold increase in the rate of PD in patients with type I GD.[4] Several studies have also found that PD is sometimes associated with carrying even a single *GBA* mutation.[2,5–10] The association was replicated in multiple studies examining PD cases from different ethnicities with a variety of *GBA* mutations.[9,11,12] A pooled analysis of case–control studies has shown that carrying a single *GBA* mutation is more common among patients with PD than among controls, with an odds ratio of 5.43[2]. *GBA* mutations are now thought to be the most common genetic risk factor for PD.[2]

Because carrier screening for *GBA* mutations is common, both through preconception screening in AJ and through direct-to-consumer genetic tests, it is imperative that an accurate PD risk estimate for *GBA* mutation carriers is established. Currently, much of the literature on this risk is derived from testing patients and families with a history of PD. One study suggests an alarmingly high risk of PD of up to 30% for *GBA* heterozygotes.[13] This may overestimate the risk of PD to *GBA* mutation carriers due to ascertainment bias in which *GBA* mutation carriers were recruited through a *GBA*/PD proband. By querying GD probands about signs and symptoms of PD in relatives, irrespective of family history of PD, we report the penetrance of PD in *GBA* mutation carriers.

## PARTICIPANTS AND METHODS

All adult (18 years or older) patients with GD with an enzymatic or molecular diagnosis of GD who were evaluated by the Comprehensive Gaucher Disease Treatment Program at the Mount Sinai School of Medicine between 2009 and 2012 were approached to participate in the study irrespective of family history of PD. To minimize ascertainment bias, the study included both subjects seen frequently at the Mount Sinai School of Medicine for treatment with enzyme infusions and follow-up

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visits as well as untreated patients who were asymptomatic or mildly symptomatic seen for follow-up. Both in-person and telephone interviews were conducted. Three patients were excluded from the study due to a personal history of dementia and an inability to provide informed consent. Contact was established with 123 adult patients with GD. Four (3.3%) declined to participate. All study procedures were approved by the Mount Sinai School of Medicine Institutional Review Board, and all participants signed an informed consent.

Ethnic background, AJ ancestry, *GBA* genotype, years of enzyme replacement therapy, and number of first-degree relatives were determined for each participant. Patients with GD were asked if they had ever been diagnosed with PD. A survey tool published by Marder et al.[14] was used to elicit family history of PD from patients with GD. The survey consists of a family history interview (FHI) that begins with six screening questions to identify PD, which includes signs of resting tremor, shuffling gait, bradykinesia, decreased arm swing, and stooped posture. Affirmative responses to any of the screening questions triggered additional follow-up questions about pathological diagnosis of PD and treatment of PD. With the use of a conservative diagnosis strategy, the survey identifies PD with a sensitivity of 95.5% and specificity of 96.2%.[14]

### Statistical analysis

Descriptive statistics (means and SD for continuous variables; percents for categorical variables) were used to report the demographics and genotype of the cohort of GD probands. The incidence of PD among participants with GD aged 60 or older was also calculated. Analyses of FHI were restricted to one proband per family (in cases of multiplex families). Main analyses were performed on the parents only because by definition they are obligatory *GBA* mutation carriers and can be viewed as independent genetic observations, given the lack of consanguinity in our sample. Kaplan–Meier survival curves were created to estimate age-specific risk of PD in parents of patients with GD (*GBA* mutation carriers). *GBA* mutation carriers were censored at their current age, age at death, or at age of onset of PD (time to event). Analyses were then repeated including parents of N370S homozygotes only, who are obligatory N370S carriers. Analyses were performed in SPSS Statistics version 19.0 software (Chicago, IL).

## RESULTS

### Participants with GD

One hundred and nineteen GD probands participated in the study. The mean age of GD probands was 50.3 years (range 18–93 years). Sixty-one participants (51.3%) were men. Most participants were of AJ ancestry: 92 (77.3%) reported all their four grandparents were AJ, and an additional 12 (10.1%) reported at least one AJ grandparent. The vast majority carried at least one N370S allele ($n$ = 113, 95.0%), and 76 (63.9%) were N370S homozygotes. Other *GBA* mutations present in this group were c.84dupG (84GG) ($n$ = 14), p.L483P (L444P) ($n$ = 8), p.R535H (R496H) ($n$ = 8), c.11511G→A (IVS2+1G→A) ($n$ = 4), p.D448H (D409H) ($n$ = 2), and p.V433L (V394L) ($n$ = 1). Eighty-two patients (68.9%) were on enzyme replacement therapy. Two patients with GD were diagnosed with PD. The first carried N370S/L444P and was diagnosed with GD at age 46 and PD at 63. He was on enzyme replacement therapy for 11 years before PD diagnosis. The second GD/PD participant was homozygous for the N370S mutation, was diagnosed with GD at 39, with PD at 57, and was on enzyme replacement therapy for 16 years before PD diagnosis. Neither had a history of splenectomy and both recalled tremor as their first PD symptom. Overall, the incidence of PD in the GD cohort was 5.4% (2/37) among participants aged 60 years or older.

### Family members

PD history was obtained on 113 unrelated families (12 participants were of multiplex families in which two siblings or a parent and a child were enrolled), including 596 first-degree family members. Relatives included 226 parents (two of whom were noninformative, adoptive parents), 184 siblings, and 186 children. Eleven (4.9%) parents, five (2.7%) siblings, and none of the children were diagnosed with PD. The genotype of the siblings affected by PD is unknown, except two who had GD and developed PD at 54 and 77. The primary analysis therefore focuses on the parents who are obligatory carriers.

Among the parents, the mean age at onset of PD was 69.3 (SD = 10.3). Age-specific risk for PD was calculated for the parents using Kaplan–Meier survival curves. Risk at age 60 was 1.0% ± 1.4%; at age 65, 2.2% ± 2.1%; at age 75, 6.8% ± 4.5%, and at age 85, 10.9% ± 7.2%. Age-specific penetrance of PD is presented in **Figure 1**. When analyses were restricted to obligatory N370S mutation carriers (parents of N370S homozygotes), risk was slightly lower: it was 1% ± 1.8% at age 65 and 8.1% ± 9.6% at age 85.

## DISCUSSION

In this study, we aimed to estimate PD penetrance among *GBA* mutation carriers. By screening all the patients with GD seen at the Mount Sinai School of Medicine between 2009 and 2012, we estimate the risk for PD to be 5.6% among these patients aged 60 or older (excluding three patients with dementia who were excluded due to the inability to provide informed consent). By conducting an FHI on all parents of patients with GD, we were able to estimate an age-specific risk for heterozygote mutation carriers. We estimate the cumulative risk by age 65 to be 2.2% and by age 85 to be 10.9%. Because preconception *GBA* testing is already widely practiced and recommended by the American College of Medical Genetics and Genomics through Jewish genetic carrier screening panels, this information can be helpful when returning genetic results to prospective parents.[15] Furthermore, two increasingly popular direct-to-consumer genetic testing companies, 23andMe and Counsyl, currently screen for four and ten *GBA* mutations, respectively, regardless of ethnic background, making these results timely for geneticists and counselors tasked with counseling carriers of *GBA* mutations on an elevated PD risk.

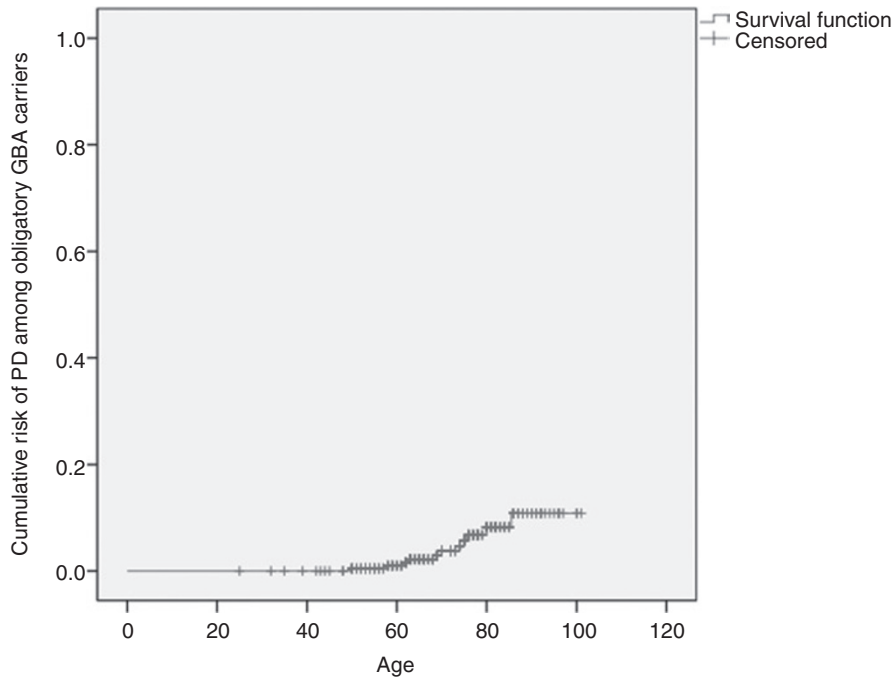


**Figure 1 Kaplan–Meier analysis of age-specific penetrance of Parkinson disease (PD) among 224 obligate carriers of glucocerebrosidase (GBA) mutations (parents of patients with type 1 Gaucher disease)**. Penetrance by age 85 is estimated to be 10.9%.

The focus of previous studies that have estimated higher PD penetrance among GBA carriers has been different; therefore, the comparison is difficult to make. Disparities may be explained either by methodological differences or by assessing carriers of different *GBA* mutations. In a French study of patients with familial PD, penetrance was estimated to be 13.7% and 29.7% at ages 60 and 80, respectively[13]; this higher penetrance may be explained by the fact that the studied population, families of *GBA* carriers with PD, had at least two risk factors. They carried a *GBA* mutation, and they were first-degree family members of a proband with PD.[13] The risk of PD among first-degree family members of patients with PD is elevated, estimated to be 5.5%.[16] In one Spanish study, 7.0% (15/213) of GD-relative *GBA* carriers reported a history of PD. The higher rate of PD in the Spanish population may be explained by the prevalence of more severe *GBA* mutations in their study, including the L444P mutation.[10] A recent study from the UK, assessing PD risk among *GBA* mutation carriers who are parents of patients with GD, had a similar study design to our study, but estimated a higher risk of PD (15% at age 80).[17] All studies have shown a consistently increased risk for PD among carriers when compared with the general population, in which PD risk is estimated at 1.0–1.5% at age 65 and ~4.9% between ages 75 and 85.[18]

The estimated risk for PD in carriers in our study is similar to the estimated risk of patients with GD derived from the Gaucher Disease Registry (7–9% before age 70 and 10–12% by age 80).[4] These findings may suggest that the mechanism linking *GBA* mutations to PD is unrelated to glucocerebroside storage, although larger studies comparing patients with GD to *GBA* carriers are required for validation.

Strengths of this study include the use of a validated family history questionnaire with strict criteria to establish PD.[14] By using obligate carriers of *GBA* mutations, we were able to ascertain the risk associated with a genetic exposure, which is exceedingly difficult to do in most other diseases. To date, this is the largest group of *GBA* mutation carriers that has been assessed for risk of PD. Another strength of our study is that 97% of patients approached to participate in the study completed the study. This provides confidence that an ascertainment bias would be unlikely in our study. With lower participation, it would have been likely that those who participated would be those who are informed about PD because of a positive family history, thereby biasing the findings towards overestimation. Furthermore, our study queried a relatively homogenous population, with 87.4% reporting at least one AJ grandparent. This is the same population that is routinely screened for *GBA* mutations and may benefit from these findings.

Our study has limitations. First, the obligate carriers of *GBA* mutations were not examined by a neurologist, and many had died; therefore, we may have overdiagnosed or underdiagnosed PD cases. Similarly, age at onset of PD was obtained by FHI. Through the FHI, we queried about classic PD motor symptoms and may have missed patients with atypical PD or Lewy body dementia, who present with cognitive decline without fulfilling the clinical criteria for PD based on the conservative diagnosis we applied. Furthermore, three patients with GD and dementia were not included because of inability to provide informed consent, which may have led to underdiagnosis of PD in GD probands. In addition, we did not genotype GD parents and therefore have not assessed for non-parenthood, although one

patient who was adopted was excluded. In addition, it is possible that some parents were GD affected and not heterozygous carriers. Although this is the largest study to date to report risk of PD in heterozygote *GBA* mutation carriers, PD events were uncommon, and therefore confidence intervals were wide.

Although *GBA* mutations may increase the risk for PD, the vast majority of patients with GD and *GBA* mutation heterozygotes will likely not develop the disease during their expected lifetimes. Future studies including a larger number of *GBA* mutation carriers may help provide an even more accurate point estimate of age-specific PD risk, and may allow counselors to stratify PD risk by the specific *GBA* mutation. These studies will aid in counseling patients found to be *GBA* mutation carriers on personal risk of PD in addition to standard counseling on reproductive risk. Although this study did not explore the biological mechanism of the incomplete penetrance of PD in carriers, exploration of genetic and environmental risk modifiers is warranted.

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## DISCLOSURE

The authors declare no conflict of interest.

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