Glucocerebrosidase Activity is not Associated with Parkinson’s Disease Risk or Severity

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ABSTRACT: Background: Mutations in the GBA gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), are risk factors for Parkinson’s disease (PD).

Objective: To explore the association between GCase activity, PD phenotype, and probability for prodromal PD among carriers of mutations in the GBA and LRRK2 genes.

Methods: Participants were genotyped for the G2019S-LRRK2 and nine GBA mutations common in Ashkenazi Jews. Performance-based measures enabling the calculation of the Movement Disorder Society (MDS) prodromal probability score were collected.

Results: One hundred and seventy PD patients (102 GBA-PD, 38 LRRK2-PD, and 30 idiopathic PD) and 221 non-manifesting carriers (NMC) (129 GBA-NMC, 45 LRRK2-NMC, 15 GBA-LRRK2-NMC, and 32 healthy controls) participated in this study. GCase activity was lower among GBA-PD (3.15 ± 0.85 μmol/L/h), GBA-NMC (3.23 ± 0.91 μmol/L/h), and GBA-LRRK2-NMC (3.20 ± 0.93 μmol/L/h) compared to the other groups of participants, with no correlation to clinical phenotype.

Conclusions: Low GCase activity does not explain the clinical phenotype or risk for prodromal PD in this cohort. © 2021 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Parkinson’s disease; LRRK2; GBA; GCase

Mutations in the GBA gene, which encodes the lysosomal enzyme glucocerebrosidase (GCase), are common risk factors for Parkinson’s disease (PD). Lower GCase activity was found not only in GBA mutation carriers, but also among idiopathic PD patients,1,2 with reduced GCase activity linked to increased alpha-synuclein aggregation.3

GBA mutations affect the phenotype of PD, with a younger age of disease onset and an increased frequency of earlier cognitive and psychiatric disorders compared to idiopathic PD (iPD).4,5 Mutations are divided into mild (mGBA), severe (sGBA), and variant (vGBA) based on their involvement in Gaucher’s disease.6 sGBA-PD is associated with worse motor, cognitive, olfactory, and psychiatric symptoms compared to mGBA-PD7,8 and a more rapid decline in these parameters.9 Moreover, the severity of PD phenotype was found to be related to the burden of GBA mutations, with homozygotes or compound heterozygotes displaying an earlier age of motor symptoms onset and worse motor, cognitive, psychiatric, and autonomic symptoms than heterozygotes GBA-PD and iPD.10 vGBA mutations are associated with PD but not with Gaucher’s disease,11 confer a high risk for cognitive impairment,12 but affect PD motor deterioration in a less severe manner.13 Penetration estimations for GBA mutations are relatively low,14 with additional
environmental and genetic modifiers including GCase activity suspected to be associated with reduced penetrance.

Despite this proposed genotype–phenotype association, the underlying pathophysiologic mechanism for GBA-PD remains unknown. While some studies show that the GBA-regulated sphingolipid pathway has an important role in PD pathophysiology, the specific role of GCase activity requires further clarification.

The G2019S mutation in LRRK2 is common among Ashkenazi Jewish (AJ) patients with PD. Conflicting reports on the role of LRRK2 and GCase activity have been published.

We aimed to assess whether GCase activity is related to PD phenotype and risk for developing disease among PD patients and non-manifesting family members of PD patients, carriers of mutations in the GBA and LRRK2 genes.

**Methods**

Participants were recruited from the BEAT-PD (TLV-0204-16), a Biogen-Tel Aviv Sourasky Medical Center (TASMC) collaborative natural history study. Patients were recruited if they were AJ, diagnosed based on the Movement Disorder Society (MDS) clinical diagnostic criteria for PD. Non-manifesting participants were recruited if they were first-degree relatives of a genetic PD patient, older than 40 years of age and were excluded if they were using dopamine-depleting medications. Additional exclusion criteria for all participants included any significant neurological or psychiatric disorders, malignancy or positive HIV, HBV, or HCV tests. The ethical committee of TASMC, according to the guidelines of the Helsinki Declaration, approved the study. All participants provided informed written consent prior to participation.

**Procedure**

Participants were genotyped for the G2019S-LRRK2 mutation and the seven founder GBA mutations as previously described. In addition, all participants were also genotyped for E326K and T369M considered vGBA (supplementary material). Participants with no detectable mutations were considered idiopathic PD (iPD) or healthy non-manifesting non-carriers (NMNC).

Performance-based measures were collected enabling the calculation of the probability for prodromal PD (likelihood ratio score) for non-manifesting participants, based on the updated MDS Task Force guidelines excluding DaT assessments and substantia nigra hyperechogenicity. Levodopa equivalent daily dose (LEDD) was calculated for all patients.

White blood count (WBC), absolute lymphocyte, monocyte, and neutrophil levels were collected. GCase analysis is described in the supplementary material.

**Statistical Analysis**

Prior to analysis, all variables were examined for normality (Shapiro–Wilk W test). Outliers were excluded when appropriate if values were two standard deviations (SDs) from the mean. Descriptive statistics were computed for all measures. Differences in sex within each cohort were evaluated using chi-square ($\chi^2$) tests. Multivariate analysis was performed to evaluate differences between groups based on disease and genetic status: The analysis was adjusted for age and sex in both cohorts and for disease duration among patients. For the GCase assessments, months in freezer were also entered as a covariate. Bivariate correlations were performed between GCase activity, laboratory, and behavioral measures. Significance was determined at $P < 0.05$ for descriptive measures and corrected for multiple comparisons using Bonferroni adjustment. Statistical analysis was performed using SPSS version 22.

**Results**

A total of 170 PD patients (102 GBA-PD [73 mGBA, 16 sGBA, 13 vGBA], 38 LRRK2-PD, and 30 iPD) and 221 non-manifesting subjects (129 GBA non-manifesting carriers [NMC] [80 mGBA, 38 sGBA, and 11 vGBA], 45 LRRK2-NMC, 15 GBA-LRRK2-NMC, and 32 NMNC) participated in this study (Table 1).

A trend for higher University of Pennsylvania Smell Identification Test (UPSIT) scores among LRRK2-PD compared to GBA-PD and iPD ($P = 0.006$, uncorrected) was detected. No significant differences between mGBA-PD and sGBA-PD were identified in any measure assessed herein.

GBA-NMC trended for higher probability scores for prodromal PD compared with the other groups of participants ($P = 0.012$, uncorrected). No difference in the probability score for prodromal PD was detected between the different GBA-NMC groups (vGBA-NMC, mGBA-NMC, and sGBA-NMC) ($P = 0.19–38.55$).

GBA-NMC demonstrated a trend for lower Montreal Cognitive Assessment (MoCA) scores compared with NMNC, LRRK2-NMC and LRRK2-GBA-NMC ($\chi^2$).
| Characteristic                  | iPD  | LRRK2-PD | GBA-PD | P value | Control | LRRK2-NMC | GBA-NMC | LRRK2-GBA-NMC | P value |
|-------------------------------|------|----------|--------|---------|---------|-----------|---------|---------------|---------|
| N                             | 30   | 38       | 102    |         | 32      | 45        | 129     | 15            |         |
| Mutation type                 |      |          |        |         |         |           |         |               |         |
| GCase (μmol/L/h)              | 4.77 ± 1.23 | 4.94 ± 1.47 | 3.15 ± 0.85 | **0.001 #** | 4.85 ± 1.43 | 4.80 ± 1.32 | 3.23 ± 0.91 | 3.20 ± 0.93 | **0.001 †** |
| Duration of storage (mo)      | 35.86 ± 2.98 | 25.51 ± 9.54 | 23.88 ± 8.68 | **0.001 $** | 32.29 ± 3.69 | 29.15 ± 5.46 | 23.62 ± 6.62 | 21.80 ± 8.18 | **0.001 ‡** |
| Age (y)                       | 65.76 ± 10.77 | 65.43 ± 9.25 | 64.91 ± 9.87 | 0.906 | 55.06 ± 10.12 | 52.49 ± 9.54 | 53.43 ± 10.71 | 50.60 ± 10.12 | 0.531 |
| Gender m/f                    | 20/10 | 23/15    | 65/37  | 0.907   | 14/18   | 24/21    | 41/88   | 4/11          | 0.060   |
| Age at diagnosis (y)          | 62.24 ± 11.07 | 62.37 ± 9.30 | 61.93 ± 10.15 | 0.970 |         |         |         |               |         |
| Disease duration (y)          | 3.52 ± 1.90   | 3.39 ± 2.54 | 3.11 ± 2.59 | 0.686 |         |         |         |               |         |
| LEDD (mg/d)                   | 342.72 ± 285.33 | 377.35 ± 397.75 | 374.37 ± 375.06 | 0.466 |         |         |         |               |         |
| MDS-UPDRS Part III            | 24.38 ± 9.50   | 19.00 ± 9.53 | 22.21 ± 12.41 | 0.368 |         |         |         |               |         |
| MDS-UPDRS total               | 41.76 ± 16.34 | 31.81 ± 17.12 | 38.39 ± 20.37 | 0.108 | 6.10 ± 4.51 | 5.51 ± 4.34 | 5.02 ± 4.47 | 4.87 ± 4.08 | 0.699 |
| Education (y)                 | 16.69 ± 3.03   | 16.84 ± 2.65 | 16.08 ± 2.97 | 0.311 | 17.55 ± 2.46 | 16.55 ± 3.18 | 17.40 ± 2.62 | 18.40 ± 2.53 | 0.095 |
| MoCA                          | 23.90 ± 3.70   | 25.08 ± 4.06 | 23.29 ± 3.98 | 0.120 | 27.13 ± 3.15 | 27.22 ± 2.56 | 25.86 ± 3.03 | 27.27 ± 2.46 | 0.006 |
| UPSIT                         | 15.65 ± 10.57  | 20.33 ± 9.35 | 15.15 ± 9.33 | 0.006 | 31.12 ± 7.05 | 32.17 ± 4.51 | 29.85 ± 6.31 | 30.64 ± 6.14 | 0.128 |
| Platelets (10^3/μL)           | 213.24 ± 54.78 | 213.11 ± 57.86 | 209.68 ± 48.66 | 0.907 | 228.48 ± 57.23 | 231.09 ± 57.13 | 234.20 ± 60.22 | 239.39 ± 71.11 | 0.958 |

(Continues)
TABLE 1

| Characteristic | iPD | Control | P-value | LRRC2-GBA-NMC | GBA-NMC | LRRC2-GBA-NMC |
|----------------|-----|---------|---------|---------------|---------|---------------|
| WBC (10^3 μL) | 6.92 ± 1.53 | 7.28 ± 2.06 | 0.583 | 6.93 ± 1.61 | 6.70 ± 1.56 | 7.01 ± 2.01 |
| GCase/WBC | 0.09 ± 0.14 | 0.14 ± 0.15 | 0.001 | 0.001 | 0.001 | 0.001 |
| GCase/monocytes | 9.71 ± 2.44 | 9.63 ± 3.11 | 0.91 | 0.001 | 0.001 | 0.001 |
| Probability | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |

Results were adjusted for multiplicity using Bonferroni correction, the original P-value is displayed. Bold type indicates significance compared with controls.

GBA-PD had significantly lower GCase activity compared to iPD and LRK2-PD (3.15 ± 0.85 μmol/L/h [95% CI 2.94–3.37], 4.77 ± 1.23 μmol/L/h [95% CI 4.42–5.31], and 4.94 ± 1.47 μmol/L/h [95% CI 4.65–5.35], P < 0.001). GCase activity did not differ between GBA-PD and sGBA-PD (3.08 ± 0.77 μmol/L/h [95% CI 2.77–3.49], P = 0.797) (Fig. 1); however, vGBA-PD had higher GCase activity compared with the two other groups (4.09 ± 0.61 μmol/L/h [95% CI 3.64–4.49]). The same results were obtained when using the GCase/WBC ratio hence we present the results of GCase activity not corrected for WBC. Age and GCase activity were not correlated and no association between GCase activity, MoCA, or the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) score was detected in the total PD cohort, or among any genetic PD subgroups.

GBA-NMC (3.23 ± 0.91 μmol/L/h [95% CI 3.04–3.42] and GBA-LRRK2-NMC 3.20 ± 0.93 μmol/L/h [95% CI 2.65–3.76]) had significantly lower GCase activity compared with LRRC2-NMC (4.80 ± 1.32 μmol/L/h [95% CI 4.41–5.27] and NMNC 4.85 ± 1.43 μmol/L/h [95% CI 4.48–5.17], P = 0.001). LRRC2-NMC had higher GCase/WBC ratio compared with the three other groups of NMC participants (NMNC, GBA-NMC, and LRRC2-GBA-NMC) (0.73 ± 0.21 [95% CI 0.69–0.78], 0.65 ± 0.28 [95% CI 0.59–0.71], 0.47 ± 0.14 [95% CI 0.45–0.50], and 0.51 ± 0.42 [95% CI 0.43–0.59], P < 0.001). A stepwise increase in GCase activity was detected between sGBA-NMC, mGBA-NMC, vGBA-NMC, and NMNC (2.98 ± 0.17 μmol/L/h [95% CI 2.64–3.31], 3.23 ± 0.11 μmol/L/h [95% CI 3.00–3.46], 4.14 ± 0.31 μmol/L/h [95% CI 3.51–4.77], and μmol/L/h 4.85 ± 1.43 [95% CI 4.07–5.36], P < 0.001) (Fig. 1). No correlations between GCase activity and age, or the MDS probability score for prodromal PD, were detected among any group of non-manifesting participants.

No difference in GCase activity between GBA-PD and GBA-NMC (3.15 ± 0.85 μmol/L/h [95% CI 2.94–3.37], 3.20 ± 0.93 μmol/L/h [95% CI 2.65–3.76], P = 0.511), mGBA-PD and mGBA-NMC (3.08 ± 0.77 μmol/L/h [95% CI 2.90–3.26] and 28.011) and 27.27 ± 2.46 (95% CI 25.53–28.32), P = 0.006, uncorrected). However, no difference in MoCA scores between the different groups of GBA-NMC was detected (vGBA-NMC, mGBA-NMC, and sGBA-NMC) (26.12 ± 0.84 [95% CI 24.45–27.80], 25.55 ± 0.31 [95% CI 24.93–26.17], and 26.41 ± 0.45 [95% CI 25.52–27.31]).
3.23 ± 0.11 μmol/L/h [95% CI 3.00–3.46], P = 0.231), or sGBA-PD and sGBA-NMC (3.13 ± 0.65 μmol/L/h [95% CI 2.77–3.49] and 2.98 ± 0.17 μmol/L/h [CI 95% 2.64–3.31], P = 0.239) were detected.

Discussion

While GCase activity among GBA-PD and GBA-NMC was low, activity among iP, LRRK2-PD, and LRRK2-NMC were within normal range. In addition, no significant difference in GCase activity was detected between mGBA-PD and sGBA-PD, and no genotype-phenotype correlations were detected between GCase activity and disease severity measures. Among NMC, a stepwise increase in GCase activity was detected between sGBA-NMC, mGBA-NMC, vGBA-NMC, and NMNC with no correlation between GCase activity and the MDS prodromal probability scores.

Pathological studies have detected reduced GCase activity in GBA-PD and iPD with the reduction in GCase activity inversely related to the accumulation of α-synuclein. A bidirectional loop between GCase activity and α-synuclein has been postulated in which reduced lysosomal GCase activity causes damage to macroautophagy and chaperone-mediated autophagy, leading to the accumulation of intracellular α-synuclein and release of α-synuclein from neurons, potentially enabling transmission to adjacent neurons. Furthermore, excessive α-synuclein levels cause a decrease in wild-type GCase trafficking to the lysosome.

An association between lower GCase activity and shorter disease duration, suggesting a more rapid progression of PD symptoms, was previously reported. However, subsequent longitudinal studies failed to replicate these results, demonstrating a correlation between GCase activity and GBA genotype, but not between GCase activity and PD phenotype.

While we detected a stepwise reduction in GCase activity between sGBA-NMC, mGBA-NMC, and vGBA-NMC, we did not find an association with risk for prodromal PD, as was previously reported. GCase activity was lower among vGBA-NMC compared to healthy NMNC as previously reported but still within normal limits. In addition, no difference in GCase activity between mGBA-PD and mGBA-NMC or between sGBA-PD and sGBA-NMC was found, indicating that GCase activity cannot be considered a biomarker for PD risk or phenotype.

GCase activity among LRRK2-PD and LRRK2-NMC was within normal limits, contrary to previous reports on patients with PD. Furthermore, GCase/WBC levels were higher among LRRK2-NMC compared with the rest of the non-manifesting participants, as was previously reported. Dual mutation carriers (LRRK2-GBA-PD) tend to exhibit a milder phenotype compared with GBA-PD. GBA-LRRK2-NMC had significantly lower GCase activity as compared with LRRK2-NMC, suggesting that the postulated LRRK2 ‘dominant effect’ is not explained by an effect on GCase activity.

Several limitations need to be addressed: the cross-sectional design of this study, the relatively small number of severe GBA-PD and sGBA-NMC participants, and the small group of vGBA-PD. The GBA gene was not sequenced but rather analyzed for specific AJ-related mutations, which represent more than 96% of the known mutations among AJ. For GCase activity measurement, we used dried blood spots, but peripheral...
blood mononuclear cells (PBMCs) or cerebrospinal fluid might have been better suited. The correlations between GCase activity and PD symptoms were performed when all patients were “ON” medications, but no data regarding “OFF” state was collected.

GCase activity does not seem to hold promise as a biomarker for disease risk or severity in PD but is rather an endophenotype of mutations in the GBA gene. An interaction between GCase activity and other mutations or environmental factors might still have relevance to PD pathogenesis.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.