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 (m*GBA*), severe (s*GBA*), and variant (v*GBA*) based on their involvement in Gaucher's disease.[6] s*GBA*-PD is associated with worse motor, cognitive, olfactory, and psychiatric symptoms compared to m*GBA*-PD[7,8] 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] v*GBA* 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] Penetrance estimations for *GBA* mutations are relatively low,[14] with additional

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environmental and genetic modifiers including GCase activity[15] 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,[3] 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.[16,17]

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.[18] 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.[4,6] 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[19] excluding DaT assessments and substantia nigra hyperechogenicity. Levodopa equivalent daily dose (LEDD) was calculated for all patients.[20]

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 (χ^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 m*GBA*, 16 s*GBA*, 13 v*GBA*], 38 *LRRK2*-PD, and 30 iPD) and 221 non-manifesting subjects (129 *GBA* non-manifesting carriers [NMC] [80 m*GBA*, 38 s*GBA*, and11 *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 (20.33 ± 9.35 [95% CI 17.54–Z23.51], 15.15 ± 9.33 [95% CI 13.19–17.05], and 15.65 ± 10.57 [95% CI 11.48–16.68], $P = 0.006$, uncorrected) was detected. No significant differences between m*GBA*-PD and s*GBA*-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 (27.10 ± 31.43 [95% CI 21.90–32.30], 8.68 ± 24.68 [95% CI 0.93–19.28], 17.09 ± 30.14 [95% CI 8.28–25.89], and 18.87 ± 25.69 [95% CI 3.61–34.11], $P = 0.012$, uncorrected). No difference in the probability score for prodromal PD was detected between the different *GBA*-NMC groups (v*GBA*-NMC, m*GBA*-NMC, and s*GBA*-NMC) (19.72 ± 9.51 [95% CI 0.89–38.55], 28.95 ± 3.52 [95% CI 21.96–35.93], and 25.34 ± 5.11 [95% CI 15.21–35.47]). *GBA*-NMC demonstrated a trend for lower Montreal Cognitive Assessment (MoCA) scores compared with NMNC, *LRRK2*-NMC and *LRRK2-GBA*-NMC (25.86 ± 3.03 (95% CI 25.37–26.32), 27.13 ± 3.15 (95% CI 26.39–28.37), 27.22 ± 2.56 (95% CI 26.38–

TABLE 1 *Characteristics of study participants*

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			N370S-67 R496H-6 84GG-7 370Rec-4 V394L-2 IVS2+1G->A-2 L4449-1 E326K-7 T369M-6				N370S-64 R496H-16 84GG-14 370Rec-10 V394L-5 IVS2+1G->A-4 L444P-5 E326K-7 T396M-4		
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 *Continued*

Characteristic	iPD	*LRRK2*-PD	*GBA*-PD	*P* value	Control	*LRRK2*-NMC	*GBA*-NMC	*LRRK2-GBA*-NMC	*P* value
WBC (10^{-3}/μL)	6.92 ± 1.53	7.28 ± 2.06	6.93 ± 1.61	0.583	7.47 ± 1.73	6.70 ± 1.56	7.01 ± 2.01	6.21 ± 1.03	0.144
GCase/WBC	0.69 ± 0.14	0.69 ± 0.19	0.48 ± 0.15	**0.001 #**	0.65 ± 0.14	0.73 ± 0.21	0.47 ± 0.13	0.51 ± 0.11	**0.001 ^, ⋆**
GCase/ monocytes	9.71 ± 2.44	9.63 ± 3.11	6.74 ± 2.76	**0.001 #**	10.28 ± 3.89	10.91 ± 4.18	7.18 ± 2.72	7.28 ± 2.16	**0.001 #**
Probability					8.68 ± 24.68	17.09 ± 30.14	27.10 ± 31.43	18.87 ± 25.69	0.012

Abbreviations: iPD, idiopathic Parkinson's disease; NMC, non-manifesting carriers; GCase, beta glucocerebrosidase; h, hour; mo, month; y, year; m, male; f, female; LEDD, levodopa equivalent daily dose; d, day; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; UPSIT, University of Pennsylvania Smell Identification Test; WBC, white blood count.
Results were adjusted for multiplicity using Bonferroni correction, the original *P* value is displayed. Bold type indicates significance after correction for multiplicity. #Difference between *GBA*-PD and iPD, *LRRK2*-PD. $Differences between iPD and *LRRK2*-PD, *GBA*-PD. ^Difference between controls, *LRRK2*-NMC and *GBA*-NMC, *LRRK2-GBA*-NMC. %Difference between controls and *LRRK2*-NMC, *GBA*-NMC, *LRRK2–GBA*-NMC. ⋆Difference between controls and *LRRK2*-NMC.

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 (v*GBA*-NMC, m*GBA*-NMC, and s*GBA*-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]).

GCase activity did not differ between men and women in any group of participants. Duration of sample storage in months differed among the total cohort ($P < 0.001$), with iPD and NMNC having the longest duration of storage. Storage time was positively correlated with GCase activity among the total cohort ($r = 0.150$, $P = 0.03$) but not among *GBA*-PD or *GBA*-NMC.

GBA-PD had significantly lower GCase activity compared to iPD and *LRRK2*-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 m*GBA*-PD and s*GBA*-PD (3.08 ± 0.77 μmol/L/h [95% CI 2.90–3.26], 3.13 ± 0.65 μmol/L/h [95% CI 2.77–3.49], $P = 0.797$) (Fig. 1); however, v*GBA*-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 *LRRK2*-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], $P = 0.001$). *LRRK2*-NMC had higher GCase/WBC ratio compared with the three other groups of NMC participants (NMNC, *GBA*-NMC, and *LRRK2-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 s*GBA*-NMC, m*GBA*-NMC, v*GBA*-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], $P = 0.511$), m*GBA*-PD and m*GBA*-NMC (3.08 ± 0.77 μmol/L/h [95% CI 2.90–3.26] and

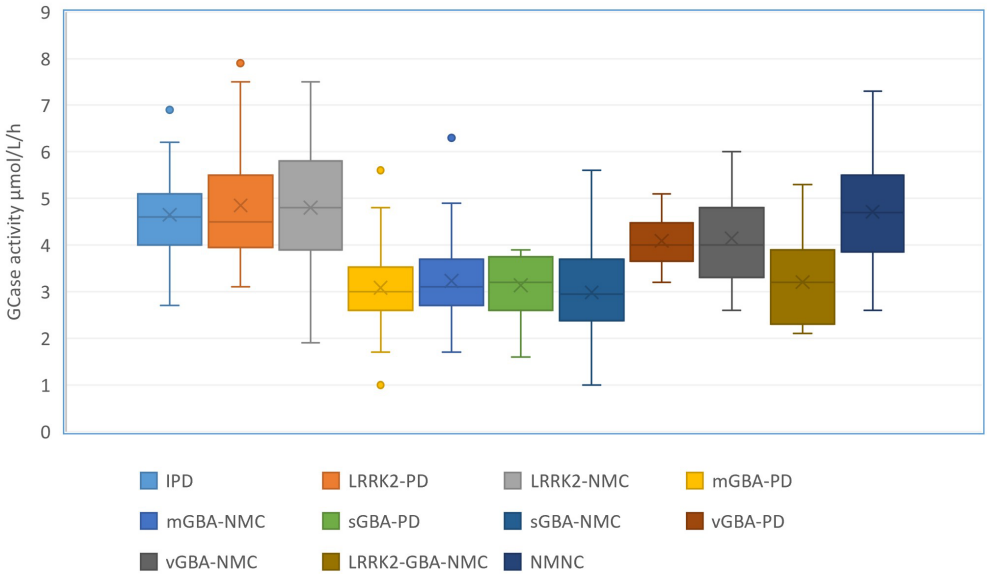

FIG. 1. Glucocerebrosidase (GCase) activity among study subgroups. The line in each box indicates the median, the 95% confidence intervals are displayed as the whiskers, and mean is depicted by the X. $P < 0.001$. IPD, idiopathic Parkinson's disease; mGBA, mild GBA; sGBA, severe GBA; vGBA, variant GBA; NMC, non-manifesting carriers; PD, Parkinson's disease. [Color figure can be viewed at wileyonlinelibrary.com]

3.23 ± 0.11 µmol/L/h [95% CI 3.00–3.46], $P = 0.231$), or sGBA-PD and s*GBA*-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 iPD, *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 s*GBA*-NMC, m*GBA*-NMC, v*GBA*-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[1] with the reduction in GCase activity inversely related to the accumulation of α-synuclein.[2] 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[21,22] 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.[23]

An association between lower GCase activity and shorter disease duration, suggesting a more rapid progression of PD symptoms, was previously reported.[17] 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.[24,25]

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.[25] GCase activity was lower among *vGBA*-NMC compared to healthy NMNC as previously reported[26] but still within normal limits. In addition, no difference in GCase activity between *mGBA*-PD and *mGBA*-NMC or between s*GBA*-PD and s*GBA*-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.[16,17] Furthermore, GCase/WBC levels were higher among *LRRK2*-NMC compared with the rest of the non-manifesting participants, as was previously reported.[27]

Dual mutation carriers (*LRRK2-GBA*-PD) tend to exhibit a milder phenotype compared with *GBA*-PD.[28,29] *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.[30] For GCase activity measurement, we used dried blood spots, but peripheral

blood mononuclear cells (PBMCs) or cerebrospinal fluid might have been better suited.[31] 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.