Cognitive performance of *GBA* mutation carriers with early-onset PD

The CORE-PD study

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Supplemental data at www.neurology.org

Supplemental Data

ABSTRACT

Objective: To assess the cognitive phenotype of glucocerebrosidase (*GBA*) mutation carriers with early-onset Parkinson disease (PD).

Methods: We administered a neuropsychological battery and the University of Pennsylvania Smell Identification Test (UPSIT) to participants in the CORE-PD study who were tested for mutations in *PARKIN*, *LRRK2*, and *GBA*. Participants included 33 *GBA* mutation carriers and 60 noncarriers of any genetic mutation. Primary analyses were performed on 26 *GBA* heterozygous mutation carriers without additional mutations and 39 age- and PD duration–matched noncarriers. Five cognitive domains, psychomotor speed, attention, memory, visuospatial function, and executive function, were created from transformed *z* scores of individual neuropsychological tests. Clinical diagnoses (normal, mild cognitive impairment [MCI], dementia) were assigned blind to genotype based on neuropsychological performance and functional impairment as assessed by the Clinical Dementia Rating (CDR) score. The association between *GBA* mutation status and neuropsychological performance, CDR, and clinical diagnoses was assessed.

Results: Demographics, UPSIT, and Unified Parkinson's Disease Rating Scale–III performance did not differ between *GBA* carriers and noncarriers. *GBA* mutation carriers performed more poorly than noncarriers on the Mini-Mental State Examination ($p = 0.035$), and on the memory ($p = 0.017$) and visuospatial ($p = 0.028$) domains. The most prominent differences were observed in nonverbal memory performance ($p < 0.001$). Carriers were more likely to receive scores of 0.5 or higher on the CDR ($p < 0.001$), and a clinical diagnosis of either MCI or dementia ($p = 0.004$).

Conclusion: *GBA* mutation status may be an independent risk factor for cognitive impairment in patients with PD. ***Neurology***® **2012;78:1434–1440**

GLOSSARY

AAO = age at onset; **BDI-II** = Beck Depression Inventory–II; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **CORE-PD** = Consortium on Risk for Early Onset Parkinson's Disease; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **MoCA** = Montreal Cognitive Assessment; **OR** = odds ratio; **PD** = Parkinson disease; **UPDRS** = Unified Parkinson's Disease Rating Scale; **UPSIT** = University of Pennsylvania Smell Identification Test.

Cognitive impairment is one of the most disabling nonmotor complications of Parkinson disease (PD). Older age, longer disease duration, and severity of extrapyramidal signs are the most important risk factors for cognitive impairment in the setting of PD.[1–4] Recently, mutations in the glucocerebrosidase (*GBA*) gene were identified as risk factors for PD,[5] affecting up to 6% of all early-onset PD cases in the United States.[6] Two independent autopsy studies found that *GBA* mutations were associated with cortical Lewy bodies, suggesting that Lewy body development may be more extensive in *GBA* carriers, and might be associated with cognitive impairment.[7,8] Among 699 participants in the Consortium on Risk for Early Onset Parkinson's Disease (CORE-PD)[9] with age at onset (AAO) <51 years, carriers of *GBA* mutations (N370S or L444P, n = 37) self-reported cognitive impairment more frequently than noncarriers. While data from the Mini-Mental State Examination (MMSE)[10] did not confirm this difference,[9] in another study, *GBA* mutation carriers performed worse than

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noncarriers on the Montreal Cognitive Assessment (MoCA).[11] In addition, a mouse model of Gaucher disease was shown to exhibit memory deficits as well as progressive accumulation of α-synuclein/ubiquitin aggregates in hippocampal neurons.[12]

In the current study, our primary goal was to examine the neuropsychological profile of *GBA* carriers compared to noncarriers. To further characterize the *GBA* phenotype, we assessed extrapyramidal features, olfaction, and depression.

METHODS

Participants. A total of 147 individuals with early-onset PD (33 *GBA* carriers and 114 noncarriers) who participated in Part II of the CORE-PD study were included. Details of the CORE-PD study have been described.[13] In brief, patients with PD, diagnosed by movement disorders specialists, were recruited for Part I of CORE-PD from 16 sites based on AAO of PD <51 years and a score on the MMSE >23. (The inclusion of individuals with MMSE >23 was incorporated to ensure that a reliable history could be obtained from each subject. There was no MMSE exclusion criterion for the follow-up, Part II examination.) A blood sample for DNA was sent to the NINDS Human Genetics Resource Center DNA and Cell Line Repository (http://ccr.coriell.org). Participants were screened for mutations in *SNCA, PARKIN, PINK-1, DJ-1, LRRK2,* and *GBA* (N370S and L444P mutations).[6] Given the higher frequency of *GBA* mutations among Ashkenazi Jews, participants who self-reported Ashkenazi Jewish ancestry were further screened for an additional 6 common *GBA* mutations (V394L, D409G, A456P, R496H, 84GG, and exon 2 IVS2 + 1) by direct sequencing. A total of 147 participants completed the Part II evaluation. The present analysis was restricted to 33 carriers of *GBA* mutations and 60 individuals who did not have any mutations in the other genes tested.[14] The *GBA* mutation carriers (n = 33) included 7 heterozygous L444P carriers, 16 heterozygous N370S carriers, 1 N370S homozygote, 2 84GG carriers, and 1 R496H carrier. Six individuals were heterozygous for *GBA* mutations and carried mutations in other PD-related genes (3 with both *GBA* and *PARKIN* mutations, 3 with both *GBA* and *LRRK2* G2019S mutations). The analyses presented here focused on the 26 heterozygous *GBA* mutation carriers who did not have *PARKIN* or *LRRK2* mutations. We also conducted sensitivity analyses including all 33 *GBA* carriers.

To ensure that the noncarriers were frequency matched to the *GBA* carriers in age and PD duration at the time of the examination, we included only noncarriers who were 47 years or older with PD duration between 7 and 25 years, similar to *GBA* carriers. This resulted in the exclusion of 21 noncarriers. The final number of included participants was 72 (33 *GBA* carriers, 39 noncarriers).

Clinical evaluation. Clinical evaluation in Part II of CORE-PD included a neurologic examination performed by a research physician, a videotaped assessment of the Unified Parkinson's Disease Rating Scale (UPDRS) evaluated by a movement disorders specialist (E.D.L.), a neuropsychological battery, and a psychiatric evaluation including the Beck Depression Inventory–II (BDI-II).[15] The University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, Inc., Haddonfield, NJ)[16] was added in 2008 and was available for 31 participants. A Clinical Dementia Rating (CDR)[17] score was assigned to each participant by a research physician (L.R.) who administered the neurologic and neuropsychological testing. A consensus panel, including the research physician (L.R.), a neurologist (K.M.), and a neuropsychologist (E.C.), assigned a clinical consensus diagnosis to each participant based on medical history, neurologic examination, neuropsychological performance, and functional impairment. Dementia diagnosis required impairment on neuropsychological evaluation in at least 2 of the following domains: memory, language, executive function, and visuospatial processing, as well as functional impairment as reflected by a CDR score greater than 0. Mild cognitive impairment (MCI) was diagnosed using Petersen's criteria, i.e., impairment in at least 1 neuropsychological domain or low scores in more than 1 domain, with no significant functional impairment.[18] None of the researchers was aware of the participants' mutation status at the time of the evaluation or consensus diagnosis.

Standard protocol approvals, registrations, and patient consents. Institutional review boards at all participating sites approved the protocols and consent procedures. Written informed consent was obtained from all participants in the study.

Neuropsychological evaluation. Details of the neuropsychological battery have been previously described[14] and are summarized in table e-1 on the *Neurology*® Web site at www.neurology.org. The battery was designed so that it was time-limited (i.e., with an administration time of approximately 30–45 minutes), could be administered in participants' homes, could be administered in English and Spanish, and could be successfully completed by patients with motor impairment. A second MMSE was performed on all participants at the time of the neuropsychological battery but was not included in the domain scores. Five cognitive domains were created based on previous research assessing predictors of cognitive decline in PD (table e-1).[14,19–20]

In a separate analysis, we further reclassified the battery into 3 domains (table e-2): executive function (including executive function, processing speed, and attention), memory (including memory tests as in table e-1 and California Verbal Learning Test-II recognition errors), and visuospatial domain (unchanged).

Statistical analysis. Demographic data, disease characteristics, MMSE, neuropsychological test performance, and UPSIT performance of *GBA* carriers and noncarriers were compared using χ^2, Fisher exact, and Student *t* tests, as appropriate. Individual neuropsychological test scores for all participants were transformed to create *Z* scores using means and standard deviations of all participants. Composite scores for each domain were computed by averaging the mean *Z* scores from the individual tests comprising each domain (see table e-1). Performance on neuropsychological testing was compared between *GBA* mutation carriers and noncarriers on individual tests and cognitive domains.

CDR scores were categorized as 0 (normal), 0.5, or 1 or higher (dementia) and compared between *GBA* carriers and noncarriers. The association between clinical diagnosis of cognitive impairment (which was made by consensus meeting based on neuropsychological performance and CDR), either MCI or dementia (dependent variable), and *GBA* mutation status (independent variable) was assessed in logistic regression models. The association was first assessed in a univariate model, and then in a multivariate model, adjusting for age in years, AAO of PD, gen-

Table 1 Demographic and disease characteristics of *GBA* carriers and noncarriers

	GBA mutation carriers (n = 24)	Noncarriers (n = 47)
Age at PD onset, y	42.9 (5.2)	43.6 (4.9)
Age at examination, y	59.0 (6.7)	57.6 (5.3)
Disease duration, y	15.4 (5.8)	14.7 (5.4)
Years of education	15.6 (2.6)	15.7 (3.3)
UPDRS-III score	35.1 (11.5)	32.5 (12.7)
Levodopa daily dose, mg	590 (347)	584 (211)
BDI-II score[b]	10.6 (7.5)	12.2 (9.2)
UPSIT score[c]	19.2 (6.8)	17.6 (5.4)
Female	30.8% (8)	41.0% (16)
History of ever smoking more than 100 cigarettes	34.6% (9 of 26)	47.2% (17 of 36)

Abbreviations: BDI-II = Beck Depression Inventory–II; PD = Parkinson disease; UPDRS = Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test.
[a] Values are mean (SD) or % (n).
[b] Higher BDI-II score indicates more signs of depression. Data available on 14 carriers and 31 noncarriers.
[c] Higher score on the UPSIT indicates better olfaction discrimination. UPSIT was available on 12 *GBA* carriers and 19 noncarriers.

der, UPDRS-III score, motor phenotype (tremor dominant vs postural instability gait difficulty),[21] and years of education.

Finally, sensitivity analyses were performed. We repeated the analyses, including all *GBA* mutation carriers (n = 33), and all noncarriers (n = 60), including those (n = 21) who were excluded for age and disease duration frequency matching.

RESULTS Demographic and disease characteristics of carriers and noncarriers of *GBA* mutations are presented in table 1. Age (frequency matched), gender, education, AAO, and BDI-II scores did not differ between carriers and noncarriers. UPSIT performance was in the severe microsmia range (score of 25 or less out of 40)[16] for 29 of 31 participants with available UPSIT data (table 1). UPSIT performance was not associated with *GBA* mutation status, neuropsychological performance, or clinical diagnosis of cognitive impairment. Raw scores on individual neuropsychological tests are reported in table 2. Three *GBA* carriers and 1 noncarrier (whose initial MMSE screen was >23) were too cognitively impaired during the Part II evaluation to complete the full neuropsychological evaluation and therefore domain scores could not be computed. When carriers' performance was compared to noncarriers', carriers scored significantly lower on nonverbal memory tests (Visual Reproduction I, Visual Reproduction II, Benton Visual Retention Test–Recognition; table 2).

MMSE scores, cognitive domain scores, CDR scores, and the clinical consensus diagnoses of cognitive impairment are reported in table 3. *GBA* carriers' MMSE performance was significantly lower than that of noncarriers. Mean scores in all 5 cognitive domains were lower in the *GBA* carrier group, reaching significance for the memory ($p = 0.017$) and visuospatial ($p = 0.028$) domains. These findings were unchanged when the neuropsychological battery was reclassified into 3 domains (memory, $p = 0.015$; executive function, $p = 0.394$; visuospatial, $p = 0.028$). *GBA* carriers were more likely to receive higher CDR scores than noncarriers ($p < 0.001$).

Among participants who received a consensus clinical diagnosis of dementia (11 *GBA* carriers, 6 noncarriers), *GBA* mutation carriers did not present a distinctive pattern of impairment in specific cognitive domains. All participants with dementia had both memory and executive impairment. *GBA* mutation carriers were more likely to receive a clinical consensus diagnosis of MCI or dementia than noncarriers ($p = 0.004$, table 3). In a univariate logistic model, *GBA* mutation status was associated with clinical diagnosis of cognitive impairment (either MCI or dementia combined) (odds ratio [OR] = 5.8, 95% confidence interval [CI] 1.7–19.9, $p = 0.005$). The association persisted when adjusted for age, gender, disease duration, UPDRS-III, motor phenotype, and education (OR = 6.2, 95% CI 1.3–29.0, $p = 0.021$).

Sensitivity analyses including all *GBA* carriers (n = 33) and all noncarriers (n = 60) revealed that *GBA* carriers were more impaired on memory ($p = 0.046$) and attention ($p = 0.007$) domains compared to noncarriers, using the 5-domain model. In this larger sample, significant differences between *GBA* carriers vs noncarriers in CDR scores ($p < 0.001$) and in the association between *GBA* mutation status and cognitive impairment ($p = 0.001$) were similar to those obtained in the primary analyses.

DISCUSSION While longitudinal follow-up of patients with PD suggests that cognitive impairment occurs in 83% of patients with PD followed up to 20 years,[22] studies have shown marked heterogeneity in the profile of cognitive impairment and in the time from onset of motor symptoms to the development of cognitive impairment.[23–25]Previous studies have shown that genetic risk factors, including variations in microtubule-associated protein tau (*MAPT*),[26] α-synuclein (*SNCA*),[26] and catechol-*O*-methyltransferase (*COMT*)[27,28]may explain some of the heterogeneity in cognitive performance in PD. We and others have shown that *GBA* mutations are associated with cortical Lewy body pathology. *GBA* mutation

Table 2 Performance of *GBA* mutation carriers and noncarriers on neuropsychological testing

Test	*GBA* carriers (n = 21)	Noncarriers (n = 46)	*p* Value
Psychomotor speed			
Trail-Making Test, part A raw score, s	51.8 (19.4)	45.7 (18.8)	0.22
Range	27–91	22–104	
Stroop Test Word Reading raw score	80.7 (20.9)	83.3 (16.4)	0.59
Range	49–113	43–126	
Stroop Test Color Naming raw score	56.6 (18.1)	57.8 (13.3)	0.76
Range	19–88	33–82	
Attention			
Trail Making Test, part B raw score, s	130.7 (61.2)	108.5 (50.2)	0.13
Range	50–240	55–220	
Stroop Color Word raw score	30.4 (12.2)	32.0 (11.1)	0.61
Range	4–52	10–51	
Memory			
CVLT Total Recall (trials 1–5) raw score	36.7 (11.8)	42.6 (10.7)	0.05
Range	10–63	17–59	
CVLT Long Delayed Free Recall raw score	7.9 (3.7)	8.8 (4.2)	0.42
Range	0–14	0–16	
CVLT Delayed Recognition Total Hits raw score	13.9 (1.5)	14.2 (1.5)	0.46
Range	11–16	11–16	
WMS-R Visual Repro I raw score	21.8 (9.9)	29.5 (7.9)	0.001
Range	0–36	0–40	
WMS-R Visual Repro II raw score	16.8 (10.9)	26.1 (8.1)	<0.001
Range	0–33	0–38	
BVRT Recognition subtest raw score	7.5 (1.4)	8.6 (1.6)	0.009
Range	5–10	2–10	
Visuospatial function			
BVRT Matching subtest raw score	9.3 (1.2)	9.8 (0.5)	0.025
Range	6–10	8–10	
Facial Recognition total raw score	20.5 (2.8)	21.6 (2.9)	0.08
Range	14–26	16–25	
Executive function			
COWAT total raw score	38.6 (13.2)	37.6 (14.1)	0.78
Range	12–58	9–63	
Category Fluency total raw score	17.0 (5.6)	17.7 (5.1)	0.60
Range	3–24	6–25	
CVLT Delayed Recognition False Positives raw score	5.1 (4.1)	3.5 (3.5)	0.11
Range	0–13	0–13	

Abbreviations: BVRT = Benton Visual Retention Test; COWAT = Controlled Oral Word Association Test; CVLT = California Verbal Learning Test; WMS-R = Wechsler Memory Scale-Revised.

status was also previously associated with dementia using *DSM-IV* criteria, after adjusting for covariates, including *APOE4* status and Alzheimer disease pathology.[7] Our findings of olfactory and cognitive impairment, most notably in nonverbal memory tasks, are all consistent with diffuse cortical neuropathology. The association between *GBA* mutation status and other nonmotor signs and symptoms of PD (e.g., REM sleep behavior disorder or hallucinations) remains to be investigated.

We may have underestimated differences in cognitive performance. Our study was probably biased toward the null: first, we compared *GBA* carriers to other affected individuals who by themselves exhibit cognitive impairment (table 2). Second, we included only participants with MMSE >23 on initial evaluation. We cannot conclude whether *GBA* mutation status is associated with PD dementia only or with dementia with Lewy body as well. Finally, because only selected mutations were genotyped, rather than complete sequencing, we may have inadvertently misclassified other *GBA* mutation carriers as noncarriers.

While *GBA* mutation status may explain a portion of the variability in cognitive performance, not all *GBA* carriers demonstrate cognitive impairment. For example, one of the *GBA* mutation carriers whose performance on neuropsychological testing was within normal range (table 3) had a motor disease duration of 21 years. Further research is required to understand additional modifiers of cognitive performance, some of which may be protective. Our study was not powered to assess for interactions with *MAPT*, *SNCA*, or *COMT* variants, or to assess for a "dose" effect. It included only a single carrier of 2 *GBA* mutations, who was excluded from all but the sensitivity analyses. It also was not powered to compare carriers of different *GBA* mutations, e.g., N370S and R496H vs L444P and 84GG. A previous study has reported that carriers of "severe" *GBA* mutations (including L444P) may have a higher risk for PD than carriers of "milder" mutations (e.g., N370); however, cognitive impairment was not assessed.[29] The neuropsychological battery, which was limited in scope, may have lacked tests that would have identified more specific executive deficits (e.g., Wisconsin Card Sorting Test). Finally, the study design, which includes a single complete neuropsychological evaluation that did not allow us to assess rate of progression, also represents a limitation.

Further research is required to assess whether nonverbal memory may be used as an early marker of cognitive impairment in mutation carriers. *GBA* mutation carriers may serve as an enriched sample to assess for early cognitive outcomes. Prospective longitudinal studies which include *GBA* mutation carriers with and without PD will help assess the time and rate of development of cognitive impairment in carriers.

Table 3 Cognitive performance of *GBA* carriers and noncarriers

	GBA mutation carriers (n = 26)[a]	Noncarriers (n = 39)[a]	*p* Value
MMSE, mean (SD)[b]	27.1 (4.9)	28.9 (1.3)	0.035
Processing speed domain	−0.17 (0.91)	0.01 (0.65)	0.382
Attention domain	−0.29 (0.93)	−0.01 (0.76)	0.218
Memory domain	−0.34 (0.75)	0.14 (0.73)	0.017
Visuospatial domain	−0.35 (1.00)	0.09 (0.58)	0.028
Executive function domain	−0.18 (0.77)	−0.02 (0.79)	0.630
CDR score, % (n)			
0	23.1 (6)	68.4 (26)[c]	0.001
0.5	46.2 (12)	10.5 (4)	
≥1 (dementia)	30.8 (8)	21.1 (8)	
Consensus clinical diagnosis, % (n)			
No cognitive impairment	15.4 (4)	51.3 (20)	0.004
Mild cognitive impairment	42.3 (11)	33.3 (13)	
Including memory	6	4	
Other	5	9	
Dementia	42.3 (11)	15.4 (6)	

Abbreviations: CDR = Clinical Dementia Rating; MMSE = Mini-Mental State Examination.
[a] Three carriers and one noncarrier were unable to complete the neuropsychological evaluation because of cognitive impairment.
[b] Domain scores are presented in *Z* scores. The lower the value, the worse the performance.
[c] CDR scores were available on 38 of the 39 noncarriers.

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