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GBA variants are associated with a distinct pattern of cognitive deficits in Parkinson disease

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Abstract

Background—Loss-of-function mutations in the *GBA* gene are associated with more severe cognitive impairment in PD, but the nature of these deficits is not well understood and whether common *GBA* polymorphisms influence cognitive performance in PD is not yet known.

Objectives/Methods—We screened the *GBA* coding region for mutations and the E326K polymorphism in 1,369 PD patients enrolled at 8 sites from the PD Cognitive Genetics Consortium. Participants underwent assessments of learning and memory (Hopkins Verbal Learning Test–Revised), working memory/executive function (Letter-Number Sequencing and Trail Making A and B), language processing (semantic and phonemic verbal fluency), visuospatial abilities (Benton Judgment of Line Orientation), and global cognitive function (Montreal Cognitive Assessment). We used linear regression to test for association between genotype and cognitive performance with adjustment for important covariates and accounted for multiple testing using Bonferroni corrections.

Results—Mutation carriers (n=60; 4.4%) and E326K carriers (n=65; 4.7%) had a higher prevalence of dementia (mutations, odds ratio =5.1; $p=9.7 \times 10^{-6}$; E326K, odds ratio =6.4; $p=5.7 \times 10^{-7}$) and lower performance on Letter-Number Sequencing (mutations, corrected $p[p_c]=9.0 \times 10^{-4}$; E326K, $p_c=0.036$), Trail Making B-A (mutations, $p_c=0.018$; E326K, $p_c=0.018$), and Benton Judgment of Line Orientation (mutations, $p_c=0.0045$; E326K, $p_c=0.0013$).

Conclusions—Both *GBA* mutations and E326K are associated with a distinct cognitive profile characterized by greater impairment in working memory/executive function and visuospatial abilities in PD patients. The discovery that E326K negatively impacts cognitive performance approximately doubles the proportion of PD patients we now recognize are at risk for more severe *GBA*-related cognitive deficits.

Keywords

cognition; *GBA*; neuropsychological tests; visuospatial; working memory

INTRODUCTION

Cognitive impairment is common in Parkinson disease (PD) and has a major impact on quality of life, caregiver distress, and mortality.[1–3] At the time of diagnosis, 19–24% of patients with PD meet criteria for mild cognitive impairment[4, 5] and up to 80% develop dementia during the course of the disease.[6, 7] The rate of cognitive decline and pattern of early cognitive deficits in PD are highly variable for reasons that are not well understood.[8, 9] The discovery of common genetic variants that contribute to this heterogeneity could shed light on the pathological processes that underlie cognitive impairment in PD. For example, the apolipoprotein E (*APOE* [OMIM 107741]) ε4 allele has emerged as an important genetic risk factor for cognitive impairment in PD. *APOE* ε4 carriers with PD are at higher risk for dementia[10–12] and prior to the onset of dementia exhibit a cognitive profile characterized by impaired performance on word list learning and semantic verbal fluency.[13]

Loss-of-function mutations in the glucocerebrosidase gene (*GBA* [OMIM 606463]) result in Gaucher disease (GD), a recessive lysosomal storage disorder. Heterozygous *GBA* mutation carriers have a substantially increased risk for developing PD.[14, 15] Furthermore, among patients with PD, *GBA* mutation carriers are more likely to develop dementia.[16–19] However, it is not clear whether PD patients with *GBA* mutations display a clear pattern of cognitive deficits as has been observed for *APOE* ε4 carriers. In addition, recent evidence from a meta-analysis of genomewide association studies (GWAS) suggests that the E326K

(rs2230288) single nucleotide polymorphism (SNP) in the *GBA* gene conveys a modest increase in risk for PD,[20] but whether this SNP influences cognitive impairment among PD patients is unknown.

In this study we sought to determine whether *GBA* mutations and E326K are associated with a distinct cognitive profile in a large, multi-center sample of patients with PD.

METHODS

Participants

We enrolled and clinically assessed 1,424 participants with PD in studies at eight sites which together comprise the PD Cognitive Genetics Consortium (PDCGC; Appendix e-1). All participants met United Kingdom PD Society Brain Bank clinical diagnostic criteria for PD (modified so that having more than one affected relative was not considered an exclusion criterion), except those from UCLA who satisfied clinical diagnostic criteria for PD as described elsewhere.[21]

To better distinguish between pathogenic mutations and population-specific SNPs we also included 62 healthy African-American controls in the study population. These individuals were enrolled in studies at UCLA, University of Pennsylvania, University of Washington, and Veterans Affairs Puget Sound Health Care System.

Standard protocol approvals, registrations, and patient consents were obtained. All study procedures were approved by the institutional review boards at each participating site.

Neuropsychological assessment

All participants with PD underwent detailed psychometric testing in the “on” state (if receiving medication). Seven tests that were administered by at least seven of the eight sites (with the exception of the Montreal Cognitive Assessment [MoCA] which was administered at six of the eight sites) were defined as the “core battery” (Table 1). We selected (*a priori*) nine variables for analysis from the core battery that represent the primary measures most commonly used in a clinical setting. These “core variables” were: total scores for MoCA, Letter-Number Sequencing Test (LNST), Trail Making Test (TMT) B-A , semantic and phonemic verbal fluency, Benton Judgment of Line Orientation (JoLO), Hopkins Verbal Learning Test-Revised (HVLT-R) total recall, HVLT-R delayed recall, and HVLT-R recognition discrimination index. Data from participants enrolled at six PDCGC sites (Appendix e-1) were reviewed at diagnostic consensus conferences, and participants were classified as demented or non-demented as previously described.[19, 22, 23] The non-demented group included participants with either no cognitive impairment or mild cognitive impairment.

Mutation screening

Genomic DNA was extracted from peripheral blood or saliva by standard techniques. Using a new method (Appendix e-2), we PCR amplified the entire *GBA* gene in a single 7,050 base pair fragment, rather than three separate fragments as has been done in previous studies,[15]

and sequenced all 11 exons and intron-exon boundaries. The sequencing success rate was 99.0%.

A mutation was considered “pathogenic” if it was previously reported in at least one patient with GD[24–27] in the homozygous or compound heterozygous state, or if it was predicted to have a clearly deleterious effect on function (e.g. frameshift or nonsense mutations). Previously published variants, such as E326K, which are not known to cause GD were classified as polymorphisms. Rare nonsynonymous substitutions that have not been reported in GD were classified as variants of unknown significance.

Statistical analysis

To reduce the influence of floor effects on cognitive test scores in patients with advanced dementia, we excluded participants who completed less than half of the tests in the core battery (n=41) as previously described.[13] Fourteen participants failed genotyping at the PCR stage. The final dataset included 1,369 patients with PD (Table 2).

We tested for association between genotype and each of the nine core psychometric variables using linear regression under a dominant genetic model adjusting for sex, years of education, disease duration, age at testing, and site. Disease duration was calculated as the difference between age at testing and either age at diagnosis (at UCLA where age at onset was not collected) or age at onset (at all other sites). We used a Bonferroni correction to adjust for the nine comparisons that were performed. Histogram and quantile-quantile plots were created for each cognitive variable and for those that were non-normally distributed (MoCA, JoLO, and HVLT-R recognition discrimination index) a squared transformation was employed to improve the fit to normality. Regression analyses were then repeated using the transformed data. We tested for differences between genotype groups for other clinical characteristics using logistic (proportion with dementia) or linear regression (age at onset, actual or calculated Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III [MDS-UPDRS III] score) adjusting for appropriate covariates. All analyses were performed using Stata version 10.0 (StataCorp, College Station, TX).

RESULTS

A total of 22 pathogenic mutations, 10 variants of unknown significance, and 3 nonsynonymous SNPs were observed among PD patients (Table 3 and Table e-1). Sixty participants (4.4%) carried one or more pathogenic mutations; 58 of these individuals were simple heterozygotes and 2 (both known to also have GD) were compound heterozygotes. Sixty-nine participants were heterozygous for E326K. Four individuals carried both a pathogenic mutation and E326K, and for the purpose of analysis were assigned exclusively to the “mutation carrier” group. The demographic features of the genotype groups are presented in Table e-2. K(−27)R has been considered a pathogenic mutation in some previous studies of PD[15] and we found this variant in six patients in our PD sample. However, all of these participants were African-American (out of a total of 29 African-American PD patients in our sample) which raised the question of whether this variant might be a SNP that is specific to populations of African origin. To address this we genotyped K(−27)R in a sample of 62 healthy African-American controls and found that 6 of them

(9.7%) carried the R allele, including one who was homozygous. Thus, we classified K(−27)R as a SNP rather than a pathogenic mutation (Table 3).

A comparison of important clinical characteristics in PD patients across *GBA* genotype groups is presented in Table 4. Age at onset of motor symptoms occurred 5.4 years earlier in mutation carriers in comparison to non-carriers ($p=1.6 \times 10^{-4}$). Mutation carriers had more severe motor symptoms, as assessed by the MDS-UPDRS III, than non-carriers ($p=0.016$). There was no significant association between E326K and either age at onset or MDS-UPDRS III score. The proportion of participants with dementia was substantially higher in both the mutation-positive group (odds ratio [OR]=5.1; 95% confidence interval [CI]=2.5–10.4; $p=9.7 \times 10^{-6}$) and the E326K group (OR=6.4; 95% CI=3.1–13.3; $p=5.7 \times 10^{-7}$).

After correction for multiple testing, mutation carriers exhibited lower performance on three psychometric tests in comparison to non-carriers: LNST (corrected p [p_c]=9.0×10^{-4}), TMT B-A ($p_c=0.018$), and JoLO ($p_c=0.0045$) (Table 5). Participants who carried E326K had significantly worse performance on the same tests: LNST ($p_c=0.036$), TMT B-A ($p_c=0.018$), and JoLO ($p_c=0.0013$). The effect sizes, as indicated by the β coefficients, were similar for the mutation-positive and E326K groups across all three tests. For example, the expected increase in mean TMT B-A time was 28.1 seconds for mutation carriers and 25.6 seconds for E326K carriers, given the same values for all other covariates. The association with scores for LNST, TMT B-A, and JoLO remained significant for both the mutation-positive and E326K groups when the analyses was restricted to whites only (n=1,284) or when *APOE* ε4 carrier status was included as a covariate (data not shown). For test scores that deviated from normality (MoCA, JoLO, and HVLT-R recognition discrimination index) analyses of the transformed data yielded similar results (data not shown).

We also compared the cognitive performance of each genotype group within the PD cohort to that of controls by calculating z-scores using published, age-adjusted normative data (Appendix e-1). As expected, the overall performance of PD patients, regardless of genotype group, was below that of controls for nearly every test (Table e-3).

DISCUSSION

Using a cross-sectional design in a multicenter sample of patients with PD we observed that both pathogenic mutations and a polymorphism (E326K) within the *GBA* gene were associated with a higher prevalence of dementia and lower performance on measures of working memory/executive function and visuospatial abilities. In addition, *GBA* mutations, but not E326K, were associated with an earlier age at onset and a higher MDS-UPDRS III score. While other studies have shown that *GBA* mutations increase risk for dementia in PD,[16–18] our study is novel in that it demonstrates (1) a link between a common *GBA* polymorphism and cognitive performance in PD, and (2) a specific cognitive profile in PD patients who carry *GBA* mutations or E326K. Because the frequency of patients with E326K or a pathogenic mutation is similar, adding E326K to the list of *GBA* variants that influence cognitive performance in PD essentially doubles the proportion of patients who are at risk for more severe *GBA*-related cognitive dysfunction.

Our findings provide further evidence that genetic variation influences the heterogeneity in cognitive profiles observed in patients with PD. This is particularly well illustrated by comparing data from the present study with those from a recent analysis of the *APOE* gene in the PDCGC cohort which utilized the same cognitive test variables.[13] *APOE* ε4 was primarily associated with lower performance on semantic verbal fluency (animals) and word-list learning (HVLT-R total recall), and these were the only two significant test variables in the subset of patients who were not demented. This pattern is more typical of the cognitive deficits seen in early Alzheimer disease (AD) than PD. In contrast, we observed that *GBA* mutations and E326K were associated with poorer performance on tests of working memory/executive function (LNST, TMT B-A) and visuospatial abilities (JoLO). Thus, *GBA* mutations/E326K and *APOE* ε4 are associated with distinct cognitive profiles in PD. This raises the question of whether there is a greater burden of pathologic changes in the temporal lobe, which subserves declarative memory[28] and semantic fluency,[29] in *APOE* ε4 carriers, and in the frontal and parieto-occipital areas, which mediate working memory/executive function[30] and visuospatial abilities,[31] in *GBA* carriers. Furthermore, since *APOE* ε4 is associated with more severe AD neuropathologic changes among patients with AD,[32] one might expect to see the same relationship in patients with PD. However, a recent PD autopsy series in the US found no correlation between *APOE* genotype and measures of AD neuropathologic changes across several brain regions.[33] Some authors have hypothesized that *GBA* mutations might be associated with more extensive cortical Lewy body disease in patients with PD.[16] A PD clinicopathological study from the UK[34] that compared brains from 17 *GBA* mutation carriers and 16 non-carriers found that a higher proportion of carriers fulfilled the McKeith criteria for diffuse neocortical Lewy body pathology, and the difference was marginally significant ($p = 0.049$). However, Lewy body scores (a semiquantitative measure of the overall cortical burden of Lewy bodies) did not differ between the two groups. Furthermore, a subsequent and more detailed analysis of these same cases using actual cortical densities of Lewy bodies concluded that there was no significant difference in “Lewy body pathology” between *GBA* mutation carriers and non-carriers.[35] Thus, it remains to be determined whether the pathological substrates that underlie cognitive impairment in PD differ among *GBA* carriers, *APOE* ε4 carriers, and non-carriers.

Several studies have reported an association between dementia and *GBA* mutations in PD cohorts. A longitudinal analysis of 262 PD patients from two independent community-based incidence studies in the UK found that *GBA* mutations substantially increased risk of conversion to dementia (relative risk, 5.45; p=0.003).[18] The projected median time to dementia for carriers was 46.0 months whereas fewer than half of the non-carriers developed dementia over the median follow-up period of 82 months. A cross-sectional study of 225 patients with PD in Spain observed a greater prevalence of dementia in mutation carriers than non-carriers (adjusted OR, 5.8; p=0.001).[17] In a cross-sectional analysis of 26 *GBA* mutation carriers and 39 non-carriers matched for age and disease duration who participated in the Consortium on Risk for Early Onset Parkinson’s Disease (CORE-PD) Study, the frequency of mild cognitive impairment or dementia was significantly higher in carriers than non-carriers (adjusted OR, 6.2; p=0.021).[16] The CORE-PD Study also compared 21 carriers and 46 non-carriers on 13 variables from 8 psychometric tests that assessed attention,

executive function, memory, and visuospatial abilities. The authors reported that carriers had lower performance for 4 test variables, but only 2 variables (Wechsler Memory Scale-R [WMS-R] Visual Reproduction I [immediate] and II [delayed]) within the "memory" domain would have remained significant if a Bonferroni correction for multiple testing had been applied. However, though the authors classified WMS-R Visual Reproduction as a test of memory, the deficits they observed among *GBA* carriers on this test could represent an impairment of memory and/or visuospatial abilities since both are required for performance of the task. In contrast, we observed associations with visuospatial abilities (measured independently from memory) and working memory/executive function, but not memory. There are several possible reasons for the discordance in findings between studies including major differences in the psychometric tests and statistical methods used, and the fact that our study had substantially greater power because of a much larger sample size. Finally, in a small cross-sectional study of PD patients who underwent a serial order task, *GBA* mutation carriers (n=15) showed significantly greater deficits in visual short-term memory/working memory than non-carriers (n=15).[36] Again, this study provides evidence for greater impairments in visual working memory among *GBA* mutation carriers, but does not provide a comparison between visuospatial abilities and aspects of memory mediated more by temporal lobe structures.

The effect of *GBA* variants on human glucocerebrosidase activity varies across a broad spectrum. In the homozygous state, "null" or "severe" mutations are thought to result in little or no activity and a severe GD phenotype, while "mild" mutations have a lesser impact on activity and cause a more benign GD phenotype.[26] Individuals homozygous for E326K do not develop GD, so it is considered a polymorphism rather than a mutation,[37] but *in vitro* studies suggest that it does decrease glucocerebrosidase activity to some degree.[38, 39] The effect of *GBA* variants on PD risk varies along a similar continuum: null/severe mutations (e.g. L444P) have the highest risk (ORs of 10–21),[40] mild mutations (e.g. N370S) confer an intermediate risk (ORs of 3–5),[40] and E326K has the lowest risk (OR of 1.7).[20] Thus, our observation that *GBA* mutations (which were roughly equally divided between null/severe and mild categories) and E326K had a similar effect on cognition (Tables 4 and 5) was unexpected. This suggests potential heterogeneity in the effects of different *GBA* variants on motor and cognitive phenotypes in PD and merits further investigation in future studies.

Our study had some limitations. Some of the cognitive measures used rely in part on motor function and thus motor symptoms might have interfered with performance on these tests. However, this was not an issue for LNST and JoLO which do not require drawing/writing and are not timed. Furthermore, we corrected TMT B for motor impairment by subtracting the TMT A score. Therefore, it is unlikely that motor symptoms impacted our findings for these three tests. In addition, participants taking medications completed testing in the "on" state to lessen the impact of motor dysfunction on test performance. Anxiety and depression can adversely affect performance on cognitive testing, and one study reported a higher prevalence of both problems in *GBA*-related PD,[40] though several other studies found no difference in measures of depression between *GBA* carriers and non-carriers.[16, 18, 41] Because we did not have adequate data on anxiety or depression in our cohort, we were not able to assess whether these non-motor features differentially impacted cognitive

performance across genotype groups. Participants in our study had a higher than average level of education, a known contributor to performance across most cognitive measures. Thus, our sample might not be fully representative of all patients with PD. Because the diagnosis of PD in our cohort was based strictly on clinical information without autopsy confirmation, some participants might have been misdiagnosed. Such non-differential misclassification would likely bias towards the null.

Further studies are needed to understand the neural basis of the cognitive profile we have observed in *GBA*-related PD. This work should include large clinicopathological studies that compare both traditional histopathological markers (e.g. Lewy bodies, neurofibrillary tangles, neuritic plaques) and molecularly specific measurements of key proteins (e.g. α-synuclein, $A\beta_{42}$, paired helical filament tau) across multiple brain regions in different *GBA* genotype groups. Neuroimaging studies, stratified by genotype, using functional MRI to examine resting-state connectivity and PET to measure regional hypoperfusion and brain amyloid (and α-synuclein if a suitable radiotracer becomes available) would provide highly complementary data. Longitudinal studies examining the rate of decline in performance within individual cognitive domains would also be useful. Knowledge gained from such endeavors could substantially accelerate progress in developing improved treatment strategies for cognitive dysfunction in PD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of cognitive tests and observed performance by domain

Cognitive domain	Test	Test description[a]	Observed score, mean (SD)[b]	Range of scores	
				Observed[b]	Possible
Global cognition	MoCA[c,d]	Brief assessment of global cognitive abilities, including orientation, attention, memory, language, abstract reasoning, and visuospatial items	24.2 (3.9)	6 to 30	0 to 30
Learning/memory	HVLT-R Total Recall[d]	Participant is asked to recall a12-item word list across 3 learning trials	21.5 (6.2)	0 to 35	0 to 36
	HVLT-R Delayed Recall[d]	Participant is asked to recall previously learned words following an approximate 20 minute delay	6.8 (3.6)	0 to 12	0 to 12
	HVLT-R Recognition Discrimination Index[d]	After delayed recall, participant is asked to determine which words were on the original list; calculated as the number of true positive minus the number of false positive responses	9.4 (2.4)	−2 to 12	−12 to 12
Verbal fluency	Semantic	Number of animals (words) generated in 1 minute	17.3 (6.1)	0 to 37	0 to NL
	Phonemic	Number of words generated that begin with the letters F, A, and S in separate 1 minute trials	36.0 (14.2)	2 to 91	0 to NL
Working memory/executive function	LNST[e]	A measure of auditory working memory in which the participant hears a combination of numbers and letters and is asked to repeat the numbers in ascending order followed by the letters in alphabetical order	8.4 (3.1)	0 to 18	0 to 21
	TMT A[f]	Test of simple graphomotor speed and non-verbal attention in which the participant is asked to sequence consecutive numbers; maximum time allowed, 150 seconds	49.1 (30.7)	12 to 150	≤150
	TMT B[f]	Test of graphomotor divided attention in which the participant is asked to sequence alternating numbers and letters; maximum time allowed, 300 seconds	142.3 (87.2)	28 to 300	≤300
	TMT B – TMT A[f]	TMT A score is subtracted from TMT B score to minimize the effects of motor disability	92.0 (68.9)	−3 to 272	≤300
Visuospatial abilities	JoLO[c]	A visual-perceptual task in which the participant is asked to match pairs of angled lines by direction and position to a display array of lines	22.4 (5.9)	0 to 30	0 to 30

Abbreviations: HVLT-R = Hopkins Verbal Learning Test-Revised; JoLO = Benton Judgment of Line Orientation; LNST = Letter-Number Sequencing Test; MoCA = Montreal Cognitive Assessment; NL = no limit; TMT = Trail Making Test.

[a] A lower score indicates poorer performance on all tests except TMT A, B, and B-A, where a higher score indicates poorer performance.

[b] Indicates scores observed in the full sample (n = 1,369)

[c] Not administered at University of California, Los Angeles

[d] Not administered at Rush

[e] Not administered at Emory University

[f] Not administered at University of Pennsylvania

Table 2

Characteristics of the study population across sites

Site	N	Male, n (%)	Mean (SD)				
			Age, at testing, y	Age, at diagnosis[a], y	Age, at disease onset[b], y	Disease duration[c], y	Education, y
Emory University	145	94 (64.8)	64.8 (8.9)	59.0 (9.7)	57.3 (9.7)	7.5 (4.4)	15.7 (2.4)
PANUC (Portland)	141	122 (86.5)	68.5 (8.0)	61.1 (10.5)	58.8 (11.1)	9.8 (6.8)	15.7 (2.8)
PANUC (Seattle)	466	300 (64.4)	67.5 (9.7)	60.6 (11.1)	58.2 (11.5)	9.3 (6.5)	15.8 (2.5)
UCLA	182	102 (56.0)	72.2 (9.5)	66.8 (9.7)	NC	5.3 (2.4)	14.1 (2.8)
University of Cincinnati	73	46 (63.0)	63.5 (10.4)	58.7 (11.2)	55.6 (11.1)	7.5 (5.6)	15.4 (2.5)
University of Pennsylvania	237	166 (70.0)	71.1 (7.6)	64.4 (8.6)	62.9 (8.9)	8.2 (5.2)	15.9 (2.4)
Rush University	89	67 (75.3)	73.4 (6.2)	NC	63.0 (7.2)	10.4 (4.6)	15.4 (3.1)
Johns Hopkins University	36	24 (66.7)	67.6 (8.8)	61.0 (10.5)	58.4 (9.2)	9.2 (5.4)	16.8 (2.4)
All Sites	1369	921 (67.3)	68.7 (9.3)	62.0 (10.6)	59.3 (10.6)	8.4 (5.7)	15.5 (2.7)

Abbreviations: NC = not collected; PANUC = Pacific Northwest Udall Center; UCLA, University of California, Los Angeles

[a] Excluding participants from Rush University, this information was not available for 32 study participants.

[b] Excluding participants from UCLA, this information was not available for 22 study participants.

[c] Calculated as the difference between age at testing and either age at diagnosis (UCLA) or age at onset (all other sites). Disease duration was not available for 22 study participants.

Table 3

GBA variants observed

Variant[a]	n
Pathogenic mutations	
IVS2+1G>A (splice site)	2
84dupG (frameshift)	3
S125N	1
T134P	1
D140H	2
R163X (premature stop)	1
N188S	1
S196P	1
G202R	1
F216Y	1
914delC (frameshift)	1
S271G	1
R359X (premature stop)	1
N370S	18
Rec3 (c1263-1317 del, D409H, L444P, A456P, V460V)	1
D409H	1
L444P	16
Rec1 (L444P, A456P, V460V)	2
Rec L444P + V460V	1
V460M	1
R463C	3
R496H	2
Variants of unknown significance	
R(−32)T	1
P(−28)S	1
R44C	1
G193E	1
R262H	1
F316I	1
G344S	1
D443N	1
V460L	1
S488T	1
Nonsynonymous polymorphisms	
K(−27)R	6
E326K	69
T369M	30

[a] Classification of variants as “pathogenic mutations,” “variants of unknown significance,” and “nonsynonymous polymorphisms” was based on the role of each variant in causing Gaucher disease, not Parkinson disease.

Table 4

Comparison of clinical characteristics across *GBA* groups

	Age at onset[a], y			MDS-UPDRS III[b]			Dementia		
	N	Mean (SD)	p^c	N	Mean (SD)	p^d	N[e] (%)	OR (95% CI)	p^f
Non-carriers	1055	59.7 (10.5)	--	1039	28.0 (12.7)	--	143/945 (15.1)	--	--
Mutation carriers	56	54.3 (8.7)	1.6×10^{-4}	55	30.4 (12.3)	0.016	16/48 (33.3)	5.1 (2.5–10.4)	9.7×10^{-6}
E326K carriers	54	57.3 (12.3)	0.22	56	29.6 (11.4)	0.17	19/47 (40.4)	6.4 (3.1–13.3)	5.7×10^{-7}

Abbreviation: MDS-UPDRS III = Movement Disorder Society Unified Parkinson's Disease Rating Scale Part III (motor examination)

[a] Not collected at University of California, Los Angeles

[b] The original UPDRS III was administered at Emory University and the University of Pennsylvania; these scores were converted to MDS-UPDRS III scores using previously published equations.[40] Neither the UPDRS III nor the MDS-UPDRS III were administered at the time of neuropsychological testing at University of California, Los Angeles.

[c] Adjusted for sex and site.

[d] Adjusted for sex, disease duration, age at testing, and site.

[e] The number of participants diagnosed with dementia is provided first, followed by the total number of participants who were assigned a cognitive diagnosis. Participants at Emory University and University of California, Los Angeles did not receive a cognitive diagnosis.

[f] Adjusted for sex, years of education, disease duration, age at testing, and site.

Table 5

Association of *GBA* variants with cognitive performance

Test	Non-carriers[a]	Mutation carriers				E326K carriers			
	N[b]	N[b]	β coefficient (95%CI)[c]	*p*	p_c	N[b]	β coefficient (95%CI)[c]	*p*	p_c
MoCA	951	47	−1.28 (−2.28 to −0.27)	0.013	0.12	51	−0.93 (−1.90 to −0.04)	0.061	0.55
HVLT-R Total Recall	1114	47	−1.50 (−3.01 to 0.01)	0.052	0.47	59	−1.93 (−3.30 to −0.56)	0.006	0.054
HVLT-R Delayed Recall	1113	46	−0.84 (−1.77 to 0.09)	0.076	0.68	59	−0.35 (−1.19 to 0.48)	0.41	>0.99
HVLT-R Recognition Discrimination Index	1103	46	−0.32 (−0.98 to 0.34)	0.35	>0.99	59	−0.20 (−0.79 to 0.39)	0.50	>0.99
Semantic Fluency	1235	60	−0.51 (−1.90 to 0.88)	0.47	>0.99	63	−1.32 (−2.67 to −0.03)	0.056	0.50
Phonemic Fluency	1206	60	−2.12 (−5.37 to 1.14)	0.20	>0.99	63	−2.09 (−5.26 to 1.08)	0.20	>0.99
LNST	1039	45	−1.57 (−2.37 to −0.78)	1.0×10^{-4}	9.0×10^{-4}	52	−1.10 (−1.85 to −0.35)	0.004	0.036
TMT B – TMT A	1003	48	28.09 (10.70 to 45.47)	0.002	0.018	58	25.58 (9.49 to 41.67)	0.002	0.018
JoLO	1058	55	−2.57 (−4.02 to −1.13)	5.0×10^{-4}	0.0045	55	−2.76 (−4.18 to −1.34)	1.4×10^{-4}	0.0013

Abbreviations: JoLO = Benton Judgment of Line Orientation; HVLT-R = Hopkins Verbal Learning Test-Revised; LNST = Letter-Number Sequencing Test; MoCA = Montreal Cognitive Assessment; *P* = uncorrected *P*-value; P_C = Bonferroni-corrected *P*-value for 9 comparisons; TMT = Trail Making Test.

All analyses are adjusted by sex, years of education, disease duration, age at testing, and site

[a] Participants who did not carry a pathogenic mutation or the minor allele of E326K.

[b] Number of participants who completed each psychometric test.

[c] Indicates the expected change in mean psychometric test score when carrying the corresponding *GBA* variant given the same values for all adjustment covariates.