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High Frequency of *GBA* Gene Mutations in Dementia With Lewy Bodies Among Ashkenazi Jews

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IMPORTANCE Mutations in the glucocerebrosidase (*GBA*) gene are a risk factor for the development of dementia with Lewy bodies (DLB). These mutations are common among Ashkenazi Jews (AJ) and appear to have an effect on the natural history of the disease.

OBJECTIVES To evaluate the clinical and genetic characteristics of an AJ cohort of patients diagnosed with DLB, assess the association of phenotype of DLB with *GBA* mutations, and explore the effects of these mutations on the clinical course of the disease.

DESIGN, SETTING, AND PARTICIPANTS Thirty-five consecutively recruited AJ patients with newly diagnosed clinically probable or possible DLB underwent genotyping for the 7 known AJ *GBA* mutations and the *LRRK2* G2019S mutation. Two patients with the *LRRK2* G2019S mutation were excluded from the final analysis. Data were collected from July 1, 2013, to July 31, 2015.

MAIN OUTCOMES AND MEASURES Assessment of clinical markers included the following standardized scales: Autonomic Scale for Outcomes in Parkinson's Disease (SCOPA-AUT), REM (Rapid Eye Movement) Sleep Behavior Disorder Single-Question Screen, Geriatric Depression Scale, and Montreal Cognitive Assessment. Motor symptoms were assessed with the Unified Parkinson's Disease Rating Scale motor part III. A subset of 15 patients also underwent assessment with the Color Trail Making Test, FAS verbal fluency, Digit Span, Hooper Visual Organization Test, and Stroop test.

RESULTS Among the 35 patients with DLB (23 men [66%] and 12 women [34%]; mean [SD], 69.6 [8.2] years), 11 (31%) were carriers of mutations in the *GBA* gene. Among the 33 patients undergoing further analysis, the *GBA* mutation carriers were younger at symptom onset (mean [SD] age, 65.7 [11.7] vs 72.1 [5.1] years; $P = .03$), had more frequent visual hallucinations that did not achieve significance (9 of 11 [82%] compared with 12 of 22 [55%]; $P = .052$), and had higher scores on the RBD questionnaire (mean [SD], 7.8 [2.2] vs 5.1 [3.3]; $P = .03$). After adjusting for age and duration of symptoms, testing revealed that *GBA* mutation carriers had poorer cognition as assessed by the Montreal Cognitive Assessment Battery (mean [SD] score, 18.75 [5.99] vs 23.23 [3.16]; $P = .03$), lower scores on tests of verbal fluency (adjusted *z* scores, 0.50 vs −2.02; $P = .02$), worse scores on tests of visuospatial function (adjusted *t* scores, 68.55 vs 79.57; $P = .046$), and higher mean (SD) scores on the Unified Parkinson's Disease Rating Scale motor part III (36.72 [10.62] vs 25.72 [10.32]; $P = .03$).

CONCLUSIONS AND RELEVANCE One in 3 AJ patients diagnosed with DLB were carriers of a *GBA* mutation, making it the most common genetic mutation identified in association with this disease and with any dementia disorder. Mutations in the *GBA* gene were associated with more severe motor and cognitive dysfunction, supporting a specific contribution of the *GBA* gene or lysosome function to this clinical syndrome.

Editorial

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Dementia with Lewy bodies (DLB) is currently believed to be the second most common form of neurodegenerative dementia after Alzheimer disease (AD).[1] The unique clinical syndrome of DLB is characterized by early cognitive and visual disturbances in association with parkinsonism and is thought to reflect early cortical involvement, specifically of the occipital and frontal cortex, much sooner than typically seen in Parkinson disease (PD).[2]

Although in the past believed to be sporadic, emerging evidence suggests a genetic contribution to DLB.[3] Heterozygosity for common mutations in the glucocerebrosidase (*GBA* [ENST00000368373]) gene have been more frequent among patients with DLB than in the general population; however, this frequency varies among different populations, from 3.5% of neuropathologically confirmed cases of DLB in a Seattle movement disorder clinic[4] to 28% in a New York cohort.[5] Phenotypically, patients with DLB and *GBA* mutations have a younger age at onset than noncarriers.[3]

A high frequency of mutations in the *GBA* gene of 19.2% has previously been described among Ashkenazi Jewish (AJ) patients with PD.[6] Given that DLB is also a synucleinopathy,[2] we aimed to ascertain the clinical and genetic characteristics of a cohort of AJ patients with DLB. First, we sought to establish the mutation carrier rate among this population. Second, we evaluated the association between the presence of *GBA* mutations and the clinical phenotype of the disease. Based on the known associations between *GBA* mutations and PD,[7-9] we hypothesized that mutation carriers would demonstrate more severe cognitive decline and parkinsonian features compared with patients with DLB who do not carry these mutations.

Key Points

Question What is the carrier rate of *GBA* mutations among Ashkenazi Jewish (AJ) patients who have dementia with Lewy bodies (DLB), and do mutation carriers have a different clinical phenotype?

Findings In this cohort of 33 consecutively recruited AJ patients with DLB, almost one-third were carriers of mutations in the *GBA* gene. In addition, mutations in the *GBA* gene were associated with more severe motor and cognitive dysfunction.

Meaning Mutations in the *GBA* gene are exceptionally common among AJ patients with DLB and have an effect on the clinical phenotype, which supports a specific contribution of the *GBA* gene or lysosome function to this clinical syndrome.

Methods

Study Cohort

The initial cohort included 35 consecutively recruited unrelated patients of AJ descent with DLB who attended the Center for Neurodegeneration at the Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel, from July 1, 2013, to July 31, 2015. Two patients found to carry the *LRRK2* G2019S mutation (ENST00000298910.11) were excluded from the final study analysis, leaving 33 patients. The mean age at symptom onset was 70.0 (SD, 78.3; range, 44-85) years, and the mean age at enrollment was 73.5 (SD, 7.5; range, 56-89) years. The 33 patients fulfilled McKeith clinical criteria for possible or probable DLB,[2] and all had onset of motor symptoms less than 1 year before the onset of cognitive decline. The Tel Aviv Sourasky Medical Center and National Helsinki committees for Genetic Studies approved the study protocols. All participants provided written informed consent before participating in the study.

Clinical and Neuropsychological Evaluation

Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale motor part III (range, 0 to 108, with higher scores indicating worse motor disability).[10] Neuropsychological tests included the Montreal Cognitive Assessment[11] to assess global cognitive function (range, 0 to 30, with higher scores indicating better cognition). The REM Sleep Behavior Disorder Single-Question Screen[12] was used to evaluate rapid eye movement sleep behavior disorder (RBD) (range, 0 to 13, with higher scores indicating more severe symptoms), and the existence of hallucinations was assessed by direct questions to the patients and the primary caregiver by an experienced neurologist from our Memory Clinic (T.S.). These assessments were completed by all patients. A subset of patients (6 GBA carriers and 9 noncarriers) additionally performed more detailed cognitive assessments, including the FAS test for verbal fluency,[13] the Stroop test[14] and Color Trail Making Test Parts A and B[15,16] to assess executive function, the Digit Span Test to assess working memory,[17] the Hooper Visual Organization Test[18] to assess visuospatial function, and the Autonomic Scale for Outcomes in Parkinson's Disease (SCOPA-AUT)[19] to assess autonomic function.

Genotyping

Genotyping of founder *GBA* mutations was performed as previously described.[9] Briefly, patients underwent testing for the 84GG, IVS2+IG>A, p.N370S, p.L444P, p.V394L, p.R496H, and RecTL *GBA* mutations using an electronic microarray (NanoChip 400; Savyon Diagnostics, Ltd). In view of the high carrier rate of *LRRK2* mutations among AJ patients, existence of the G2019S mutation was also examined. Two patients with DLB were carriers of the G2019S *LRRK2* mutation and were excluded from the present analysis.

Statistical Analysis

Descriptive characteristics were examined for all patients. Neuropsychological measures were examined for normalcy using box plots and histograms. Cognitive tests were transformed into z scores or *t* scores based on age and level of education for all neuropsychological tests. Differences in cognitive measures between the groups (carriers vs noncarriers) were examined using mixed models with adjustment for age, sex, years of education, and disease duration. Corrections for multiple comparisons were made using the Hochberg-Benjamini method based on predefined cognitive domains.[20] We used SPSS software (version 21; SPSS, Inc) for all data analyses, with the α level set at .05.

Table 1. Patient Demographic Characteristics and Questionnaire Results

Characteristic	Patient Group		*P* Value
	Noncarriers (n = 22)	*GBA* Mutation Carriers (n = 11)	
Age, mean (SD) [range], y			
At testing	75.0 (5.0) [67-86]	70.3 (10.6) [56-89]	.09
At onset	72.1 (5.1) [63-85]	65.7 (11.7) [44-85]	.03
Sex, No. (%)			
Male	15 (68)	7 (64)	.40
Female	7 (32)	4 (36)	
Disease duration, median (range), y	2.9 (0-7)	4.2 (1-9)	.06
Educational level, median (range), y	13.8 (10-21)	14.1 (11-18)	.35
Hallucinations, No. (%)	12 (55)	9 (82)	.052
RBD1Q score, mean (SD)	5.1 (3.3)	7.8 (2.2)	.03
Presenting symptoms, No. (%)			
Motor	3 (14)	4 (36)	.20
Cognitive	6 (27)	4 (36)	.62
Concurrent motor and cognitive	13 (59)	3 (27)	.08

Abbreviations: *GBA*, glucocerebrosidase gene; RBD1Q, REM (Rapid Eye Movement) Sleep Behavior Disorder Single-Question Screen.

Table 2. Neuropsychological Test Results

Test	Noncarriers	*GBA* Mutation Carriers	*P* Value
Global cognitive function, mean (SD)			
MoCA raw score[a]	23.23 (3.16)	18.75 (5.99)	.03[b]
Executive function domain			
TMT part A, *z* score[c]	−5.02	−7.27	.22
TMT part B, *z* score[c]	−4.10	−5.68	.27
TMT B − A, *z* score[c]	0.92	2.53	.09
Stroop[c]	21.38	18.8	.16
Working memory domain			
FAS verbal fluency, *z* score[c]	0.50	−2.02	.02[b]
Digit Span, S score	8.53	7.85	.13
Visuospatial domain			
HVOT, *t* score[d]	68.55	79.57	.046[b]

Abbreviations: *GBA*, glucocerebrosidase gene; HVOT, Hooper Visual Organization Test; MoCA, Montreal Cognitive Assessment; TMT, Trail Making Test.

[a] Scores range from 0 to 30, with greater scores indicating worse cognitive impairment.

[b] Significant even after multiple-comparison correction.

[c] Higher *z* scores indicate a greater SD from the norm. Lower scores on the test indicate worse performance.

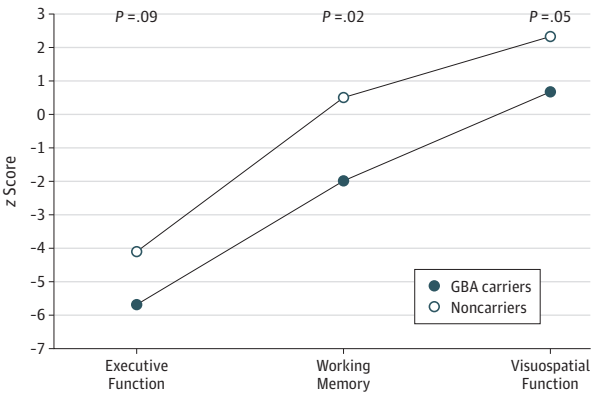
[d] Scores range from 41 to 104, with higher *t* scores indicating higher likelihood of neurologic dysfunction.

Results

Among the 35 AJ patients with DLB, 23 were men (66%) and 12 were women (34%), with a mean (SD) age of 69.6 (8.2) years. Eleven patients (31%) were carriers of mutations in the *GBA* gene. Nine patients carried the N370S mutation, considered a mild mutation; 1 carried an L444P mutation, and 1 carried a RecTL/N370S mutation, both considered severe mutations. Two patients carried the G2019S mutation in the *LRRK2* gene and were therefore excluded from any further analysis. Twenty-nine patients fulfilled criteria for probable DLB, and 1 patient in the carrier group and 3 from the noncarrier group met criteria for possible DLB. The mean (SD) age of cognitive or motor symptom onset was younger among the *GBA* mutation carriers than the noncarriers (65.7 [11.7] vs 72.1 [5.1] years; *P* = .03). The mode of clinical presentation in each group with motor symptoms first, cognitive symptoms first, or concurrent cognitive and motor symptoms is given in **Table 1.** Briefly, a higher percentage of patients from the noncarrier group presented with concurrent symptoms at onset. More frequent visual hallucinations were found in the *GBA* mutation carrier group (9 of 11 [82%] vs 12 of 21 [55%]; *P* = .052). The presence and severity of RBD was higher in *GBA* mutation carriers than in noncarriers, with carriers presenting with higher mean (SD) scores on the REM Sleep Behavior Disorder Single-Question Screen (7.8 [2.2] vs 5.1 [3.3]; *P* = .03) (Table 1). There were no significant differences between groups in autonomic symptoms as reflected by the SCOPA-AUT Questionnaire (*P* = .15). Use of acetylcholinesterase inhibitors also tended to be higher among the *GBA* mutation carriers (8 of 11 [73%] vs 10 of 22 [45%]; *P* = .06).

Poorer cognitive function was observed in *GBA* mutation carriers compared with noncarriers as assessed by the Montreal Cognitive Assessment (mean [SD] raw score, 18.75 [5.99] vs 23.23 [3.16]; *P* = .03) after adjusting for age, sex, level of education, and symptom duration. No differences were observed between the groups in the Stroop, Digit Span, or Color Trail Making tests when analyzed separately or when the differences were evaluated (**Table 2**). However, after adjusting for symptom duration, age, sex, and years of education, carriers had lower scores on the phonemic verbal fluency test (ad-

Figure. Differences in Cognitive Function Between Carriers and Noncarriers of *GBA* Mutations



The population includes 33 patients with dementia with Lewy bodies, including 11 carriers and 22 noncarriers of *GBA* mutations. We compared *z* scores on neuropsychological tests of different cognitive domains between the groups. Executive function was measured using the Color Trail Making Test A and B; working memory, the FAS test for verbal fluency; and visuospatial function, the Hooper Visual Organization Test. All scores were adjusted for age, sex, years of education, and disease duration. Error bars represent SEM.

justed *z* scores, 0.50 vs −2.02; $P = .02$) and on the Hooper Visual Organization Test for assessment of visuospatial function (adjusted *t* scores, 68.55 vs 79.57; $P = .046$) (**Figure**). Furthermore, *GBA* mutation carriers presented with higher scores on the Unified Parkinson's Disease Rating Scale motor part III than noncarriers, which reflected more marked extrapyramidal signs (mean [SD], 36.72 [10.62] vs 25.72 [10.32]; $P = .03$).

Discussion

The aim of this study was to ascertain the clinical and genetic characteristics of an AJ cohort of patients diagnosed with DLB and to evaluate the association between the characteristics of the disease and the presence of *GBA* mutations. The AJ group is of specific interest owing to the increased carrier frequency of *GBA* mutations and the previously described link between *GBA* mutations and the risk and nature of DLB. Our results revealed an exceptionally high frequency of mutations in the *GBA* gene (31%) among AJ patients with DLB compared with a carrier rate of 6.35% in the general AJ population. Because the recruitment was consecutive from an outpatient movement disorders and memory clinic, we believe that our observation reflects the real frequency among the AJ population with DLB. In addition, patients with DLB who carried *GBA* mutations had a more aggressive disease course as reflected by the younger age of symptom onset, more frequent hallucinations, and poorer performance in cognitive and motor tests.

Although the difference did not reach significance, the higher percentage of *GBA* mutation carriers who were taking acetylcholinesterase inhibitors at the time of testing is of interest. The difference may be because the severity of the cognitive decline is more marked in this group and may have led to the commencement of this therapy sooner. This finding strengthens our results by demonstrating that despite the use of acetylcholinesterase inhibitors, *GBA* mutation carriers still had significantly more cognitive impairment than noncarriers. If none of the patients had taken acetylcholinesterase inhibitors, we may have observed even greater differences in cognition between groups.

Based on the observed association between *GBA* mutation status and hallucinations as well as more severe cognitive disturbances, a specific association between the distribution of Lewy body abnormalities pathology and the *GBA* gene may exist. Visual hallucinations have been associated with increased numbers of Lewy bodies in the anterior and inferior temporal lobe and neuritic degeneration in the CA2 to CA3 region of the hippocampus in DLB,[21] which suggests that these regions are pathologically more vulnerable when the *GBA* gene is mutated, even in only 1 allele. The *GBA* mutation may not only result in accelerated synuclein-associated neurodegeneration but specific neurons may be more dependent on lysosomal activity and thereby may exhibit dysfunction earlier in the course of the disease. In support of this link between synuclein aggregation in the hippocampal CA2 to CA4 neurons and mutations in the *GBA* gene, positive synuclein inclusions have been observed in the hippocampal CA2 to CA4 neurons, even in patients with Gaucher disease who developed PD.[22]

Of special interest is—to our knowledge—our first ever reported association between RBD and *GBA* mutation status among a DLB cohort. This association has been described in PD cohorts and among patients with RBD[23] but never in patients with DLB. The present observation consolidates the association between RBD and the *GBA* gene to further support a more specific role of the *GBA* gene and possibly the lysosome in the neural network responsible for the development of RBD.

Along the same lines of the unique association between the *GBA* gene and specific neural networks is our present observation that patients with DLB who carry *GBA* mutations performed worse on frontal executive function testing (phonemic verbal fluency). Functional neuroimaging studies have previously reported increased activation in the dorsolateral prefrontal cortex during phonemic verbal fluency tasks.[24] The dorsolateral prefrontal cortex is one of the main projection sites of the dorsal striatum,[25] a brain area known to have a higher burden of α-synuclein abnormalities in DLB when compared with PD,[26] which may in part explain why these deficits have not been observed among patients with PD and *GBA* mutations.[27,28] Functional magnetic resonance imaging studies examining brain activation areas while performing the Hooper Visual Organization Test reported increased activation in the visual association areas,[18] which have been shown to be pathologically involved in DLB.[29] Patients with PD who are *GBA* mutation carriers have been shown to have poorer visuospatial function,[27] supporting a selective vulnerability of these pathways to mutations in the *GBA* gene. Furthermore, in detailed testing of visual short-term memory, *GBA* mutation carriers with and without PD show an increased susceptibility to visual memory interference, once again linking pathologic features in this system with these specific genetic

mutations.[30] Our findings complement these earlier reports by demonstrating poorer performance on tests of visuospatial function in *GBA* mutation carriers with DLB. In fact, our findings of worse performance in these tasks may reflect more severe damage to these networks among *GBA* mutation carriers, which supports our proposal that not all brain regions or networks rely to the same extent on lysosomal activity. Another possible explanation for the specific clinical profile among *GBA*-mutated DLB is not vulnerability of the neurons or networks but less effective compensation or reserve in those regions or networks. Although many similarities are found in the cognitive profiles of patients with PD and *GBA* mutations and those with DLB and *GBA* mutations, lower cognitive reserve among the patients with DLB may explain some of the differences in performance that we have observed.

The precise mechanism by which *GBA* mutations lead to accumulation of α-synuclein remains poorly understood, and loss-of-function and gain-of-function theories have been proposed. Some of the work pointing toward a loss-of-function mechanism comes from in vitro studies, which found that decreased glucocerebrosidase activity leads to aggregation of abnormally folded α-synuclein[31] and that perturbation of glucocerebrosidase activity in mice neuroblastoma cells leads to α-synuclein aggregation.[32] In addition, a bidirectional effect has been postulated whereby the abnormally folded α-synuclein leads to further inhibition of glucocerebrosidase activity, which forms a bidirectional loop and a self-propagating disease.[31] Support for the gain-of-function theory comes from the demonstration that several *GBA* mutations lead to a misfolded glucocerebrosidase protein. Several mechanisms by which misfolded glucocerebrosidase might contribute to parkinsonism have been proposed. Reduced α-synuclein degradation due to lysosomal insufficiency, impairment of other autophagic pathways necessary for preventing accumulation of α-synuclein, or overwhelming of the ubiquitin-proteasome pathway may cause a delay in the degradation of accumulated α-synuclein. Augmentation of glucocerebrosidase activity has been attempted in animal disease models with promising results[32,33]; however, no controlled trials have been undertaken on humans as yet.

The main limitation in our study is the cohort size. Dementia with Lewy bodies is a disease known to be underdiagnosed and, because it is a progressive neurodegenerative process, patients have to be recruited and examined during the stage of their disease when they are able to provide informed consent and perform cognitive testing. Despite the size of the cohort, an important strength of the study is the consecutive recruitment from an outpatient clinic, which allows for the assumptions relating to genotype frequency and phenotypic manifestation. A further limitation is the cross-sectional aspect to the design, which unfortunately does not allow us to comment on the rate of progression of disease in *GBA* mutation carriers compared with noncarriers.

Conclusions

Our study demonstrates that *GBA* mutations are exceptionally common among AJ patients with DLB. Furthermore, the presence of these mutations appears to have an effect on the phenotype of disease. Several important questions remain to be answered. Given the high carrier rate of these mutations in the general AJ population but the fairly low penetrance, the understanding of what leads to the development of disease in some carriers but not in others has yet to be explored. An interesting and puzzling fact is that some AJ mutation carriers develop DLB, others develop PD, and most will have no disease until 70 or 80 years of age. The association between the type of *GBA* mutation and the phenomenology constitutes another area of special interest. In PD, investigators[6] have reported the stronger contribution of severe GBA mutations to the risk and to earlier age of motor symptoms onset and a distinct phenotypic disease manifestation. In our present small sample, we were unable to explore these differences, and future studies should investigate the difference in DLB phenotype based on the type of mutation. The association between *GBA* mutation type and the clinical syndrome might reflect a complex relationship between *GBA* and α-synuclein abnormalities, possibly mediated by other genes or interactions with the environment.

The fact that *GBA* mutations appear to have such a significant effect, even within a small cohort of patients, implies that these mutations may have a role in the pathologic process of this disease. Understanding the effect of these mutations on glucocerebrosidase and lysosomal function may hold the key to the development of neuroprotective therapies in this disease in the future. Understanding the mechanisms by which these mutations are associated with DLB is instrumental in paving the way to the development of personalized treatments in the future.

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Study concept and design: Ash, Gurevich, Bregman, Giladi.
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