project for their help. S.V., A.M., A.M.M.S., J.W.J.E., and M.A.J.T. are part of the European Reference Network Rare Neurological Disorders (ERN-RND). This work was supported by the European Fund for Regional Development of the European Union in collaboration with the province of Fryslan (grant number 01492947) and a ZonMW TOP Grant (grant number 91218013).

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.

Effect of GBA1 Mutations and APOE Polymorphisms on Survival and Progression Among Ashkenazi Jews with Dementia with Lewy Bodies

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ABSTRACT: Background: Glucocerebrosidase 1 *(GBA1)* mutations are associated with reduced survival in Parkinson's disease but their effect on survival in dementia with Lewy bodies (DLB) is unclear.

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Relevant conflicts of interest/financial disclosures: All authors report no conflict of interests pertaining to the article.

Funding agency: The research was funded by internal hospital grants.

Received: 3 April 2024; **Revised:** 28 June 2024; **Accepted:** 12 August 2024

Published online 30 August 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30003

Objective: To assess the impact of *GBA1* mutations on survival among Ashkenazi Jews with DLB, while controlling for *APOE* status.

Methods: One hundred and forty participants from Tel Aviv Medical Center, Israel were genotyped for *GBA1* mutations and *APOE* polymorphisms. Survival rates and follow-up cognitive screening scores were analyzed.

Results: *GBA1* mutation carriers had a two-fold increased risk of death (HR = 1.999), while *APOE* status did not independently affect survival. In a subset of patients with available clinical data (N = 63), carriers of the *APOE ε4* allele showed faster cognitive deterioration, while *GBA1* mutation carriers also declined more rapidly albeit not significantly.

Conclusion: Understanding the genetic effects on survival and progression is crucial for patient counseling and inclusion in clinical trials.

Dementia with Lewy bodies (DLB) is a clinically heterogeneous neurodegenerative disease characterized by the accumulation of Lewy bodies and neurites and often by concomitant Alzheimer's disease (AD) pathology.[1] Mutations in the *GBA1* gene are the most common genetic factor associated with Parkinson's disease (PD) and are frequent among patients with DLB.[2-4] Previous studies show that PD and DLB patients with *GBA1* mutations have younger motor symptom onset and a more severe disease phenotype.[5,6] In PD, carriers of *GBA1* mutations have a more aggressive disease course, with faster progression and reduced survival[7-10]; however, the effect of *GBA1* mutations on survival in DLB is still unclear, with conflicting results in the literature.[11,12] The *APOE ε4* allele is a significant risk factor for developing AD,[13] and is the top hit in genome association studies in DLB.[14] A study examining the influence of these genetic factors in PD demonstrated that carriers of either *GBA1* mutations or the *APOE ε4* allele had faster cognitive decline and were at a higher risk of progressing to dementia than non-carriers. Furthermore, carriers of both genetic factors had the most significant risk of progressing to dementia.[15] In a previous study in our cohort, which included follow-up data until the start of 2020, we did not find a clear effect on cognitive deterioration of either factor.[5] We were also unable to examine survival due to insufficient years of follow-up. The aim of the current study was to examine the effects of these common genetic factors on survival and progression in a cohort of Ashkenazi Jewish (AJ) patients with DLB, known to have high carrier rates of *GBA1* mutations.[4]

Methods

Study protocols were approved by the Institutional Review Board (IRB) Committees for Genetic Studies. Participants provided informed consent. Survival analysis included consecutively recruited patients with DLB of AJ descent, who attended the Tel Aviv Medical Center between July 2013 and November 2023. Baseline research evaluation, including comprehensive neuropsychological and motor testing, was conducted for all patients. The results of these evaluations for 100 of the patients included in this study appeared in our previous publication.[5] Follow-up Mini-Mental State Examination (MMSE) data were collected in routine clinic visits, which varied between 4 and 22 months and were not conducted at set intervals. Due to the tertiary nature of our center, patients were also followed up in the community, with less frequent visits to the hospital clinic. Death was confirmed via the Israeli National Registry in which date but not cause of death are available.

Genotyping of founder *GBA1* mutations was performed as previously described.[16] Briefly, patients were tested for the 84GG, IVS2 + IG > A, p.N370S, p.L444P, p.V394L, p.R496H, and 370Rec GBA1 mutations, using the "Gaucher Kit" (Catalog number 800672, Savyon Diagnostics, Ashdod, Israel, https://www.savyondiagnostics.com/product/nanochip-gaucher). The E326K and T369M *GBA1* variants were genotyped using gene-specific TaqMan assay, followed by Sanger sequencing of polymerase chain reaction (PCR) products, to confirm carriers. *GBA1* pathogenic variants were divided into three groups: (1) non-Gaucher disease (GD) causing (E326K and T369M), (2) variants associated with mild Gaucher disease (N370S and R496H), and (3) variants associated with severe Gaucher disease (84GG, Ivs2, V349L).[17] Existence of the LRRK2 G2019S mutation was also examined. All samples were genotyped for rs429358 and rs7412, using TaqMan assays (C___3084793_20 and C____904973_10, respectively; Applied Biosystems) to establish their APOE haplotypes. Samples that carried E2 or E4 haplotypes were also Sanger sequenced as a second independent method to confirm ApoE haplotypes. Primers used to amplify the ApoE specific fragment for sequencing were: forward 5′ GGCACGGCTGTCCAAGGAGCT 3′ and reverse 5′ GCCCCGGCCTGGTACACTGC 3′.

Statistical Analysis

Descriptive statistics (means, standard deviations, Student's *t*-test, and ANOVA for continuous variables; proportions, frequencies, and chi-square test for categorical variables) were used to compare the demographics of *GBA1* carriers and non-carriers. In survival analyses, time to event was defined as survival in months. Participants were censored at the age

of our last contact if they did not reach an event (death). We used log-rank tests and Cox proportional hazards models, adjusted for sex and age at symptom onset, to compare survival between *GBA1* carriers and non-carriers and between *APOE ε4* carriers and non-carriers.

In order to assess deterioration in MMSE scores per year on an individual basis, we subtracted the last MMSE score recorded for each patient from the first MMSE score recorded and divided it by years of follow-up. We used an analysis of covariance (ANCOVA) with *GBA1* mutations and *APOE* polymorphisms as between-subject factors and the deterioration per year as the dependent variable, with age at onset, disease duration until first MMSE, sex, and years of education as covariates. Eta squared served to estimate effect size. All analyses were conducted with Statistical Package for the Social Sciences (SPSS) software (Version 29; SPSS, Inc., Chicago, IL, USA), and the alpha level was set at 0.05.

Results

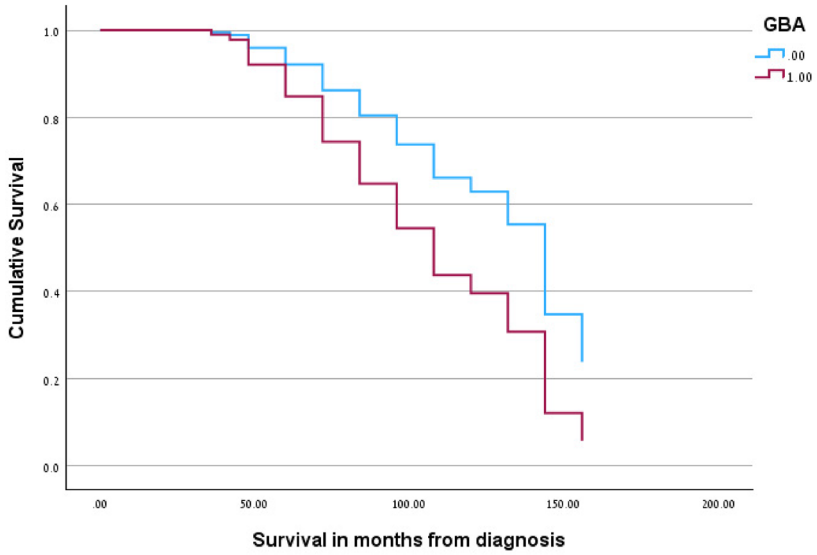
Participants' Survival Analysis

One hundred and forty patients (n = 106, 75.7% men) were included in the survival analysis. Of these, 45 (32.1%) were carriers of mutations in the *GBA1* gene, 38 carried mutations considered to be mild and 5 carried mutations considered severe, 1 was heterozygote for the T369M variant, and 1 was heterozygote for the E326K variant. Forty-two (30%) patients were carriers of an *APOE ε4* allele and, of these, 11 patients (7.8%) were carriers of both a *GBA1* mutation and the *APOE ε4* allele (Table 1). There were no LRRK2 mutation carriers in the cohort. One of the patients who was a *GBA1* mutation carrier ended her life by assisted suicide overseas and was therefore excluded from further analyses. During the 2013–2023 period, 54 of the remaining 139 patients died, 20 of whom were *GBA1* mutation carriers. Multivariable analysis, performed after adjusting for sex and age at onset, showed a significantly increased risk of death in *GBA1* carriers compared with non-carriers (hazard ratio [HR] = 1.999, $P = 0.02$; Fig. 1). *APOE* status had no independent effect on survival or age of onset (HR = 1.226, $P = 0.482$). The effect of *GBA1* mutations on survival persisted, albeit with borderline significance, even when the severe mutation carriers were excluded (HR = 1.830, $P = 0.05$), demonstrating an effect of all *GBA1* mutations on survival. Most patients died in the community, and therefore exact cause of death was unavailable in hospital records. As was found in previous studies, whole-group analysis demonstrated that the *GBA1* mutation carriers were younger at symptom onset (mean [SD] age, 66.93 [8.56]vs. 70.37 [6.20] years; $t = 2.394$, $P = 0.020$). Within the group of patients who died (N = 54), age of onset did not differ significantly between *GBA1* and non-*GBA*1 carriers (mean [SD] 68.4 [9.06] vs. 71.63 [6.131] years; $t = 1.415$, $P = 0.168$) nor did age at death (mean [SD] 76.2 [7.66] vs. 79.14 [6.2]; $t = 2.780$, $P = 0.15$).

TABLE 1 *Patient demographics.*

Parameter	*GBA1* mutation carriers (n = 45)	*GBA1* non-carriers (n = 95)	*P*-value
Sex (male)	32 (71.11%)	73 (76.84%)	0.53*
APOE *ε4* carriers	11 (24.44%)	31 (32.63%)	0.43*
ε3/ε4 carriers	9 (20.00%)	29 (30.52%)	
ε4/ε4 carriers	2 (4.44%)	2 (2.10%)	
Age at onset[a] (years) (n = 139)	66.93 [8.56]	70.37 [6.20]	0.02**
Died (n = 140)	21 (46.66%)	34 (35.78%)	
Patients who died (n = 54)			
Survival after diagnosis until death (months)	93.60 [30.80]	90.17 [33.43]	0.71**
Age at death (years)	76.20 [7.66]	79.14 [6.20]	0.15**
Age at onset[a] (years)	68.40 [9.06]	71.63 [6.13]	0.16**
Sex (male)	12 (57.14%)	28 (82.35%)	0.18*
APOE ε4 carriers	6 (28.57%) all of them *ε3/ε4* carriers	13 (38.23%) all of them *ε3/ε4* carriers	0.57*

*Chi-square test.
**Independent sample two-sided *t*-test.
[a]Age at onset refers to age at symptom onset.



GBA1 mutation carriers	95	89	75	61
Non-*GBA1* mutation carriers	44	40	29	24

FIG. 1. Cox proportional hazard regression for survival in months from diagnosis in *GBA1* mutation carriers and non-carriers adjusted for sex and age at onset. [Color figure can be viewed at wileyonlinelibrary.com]

Participants' Follow-Up Analysis

Follow-up MMSE data were available for 63 of the 140 participants. Of these subjects, 19 were carriers of GBA1 mutations, 15 were carriers of *APOE ε4* polymorphisms, and 8 patients were carriers of both genetic factors. Average disease duration at baseline was 37.57 months (SD 25.75). Average number of clinic visits was 3.78 (SD 1.90), and average time between visits was 13.7 months (SD 8.5). Average follow-up time was 36.7 months (SD 22.62). Average deterioration on the MMSE per year was 0.22 (SD 0.31) points. ANCOVA revealed that carriers of the *APOE ε4* allele had a faster cognitive deterioration than non-carriers: 3.90 vs. 2.04 per year, $F(1,62) = 5.32$, $P = 0.025$, $\eta 2 = 0.88$. Carriers of the *GBA1* mutation deteriorated more rapidly compared with non-carriers with a trend towards significance: 3.44 vs. 2.17 per year, $F(1,62) = 3.85$, $P = 0.055$, $\eta 2 = 0.066$. The interaction between the two mutations was not significant: $F(1,62) = 2.03$, $P = 0.159$, $\eta 2 = 0.036$.

Discussion

We found that AJ patients with DLB who are carriers of *GBA1* mutations had a two-fold increased mortality risk. While some prior studies have not shown reduced survival in DLB patients with *GBA1* mutations, our findings align with numerous studies in PD patients that indicated reduced survival among *GBA1* mutation carriers.[7,8] In the present cohort, we found no main effect of the *APOE ε4* allele on survival, in contrast to another study that found both a lower MMSE at baseline and a shorter disease duration among *APOE ε4* carriers,[11] with no effect of *GBA1* mutations. Differences in the type of *GBA1* mutation across cohorts may explain the variations. The Dutch cohort had more *E326K* carriers, a milder variant unrelated to Gaucher disease in homozygous form. In contrast, our AJ cohort were mainly *N370S* carriers which is linked to type 1 Gaucher disease. Furthermore, the Dutch study did not find a more severe cognitive syndrome in *GBA1* mutation carriers, unlike other cohorts,[3,5,18] and thus patients might have been less severely affected at baseline. Another study on survival in patients with DLB has shown that the *APOE ε4* allele was associated with shorter survival, but only in individuals with lower hippocampal volumes at baseline.[12]

An analysis of a subgroup of patients for which clinical follow-up data were available demonstrated that the presence of the *APOE ε4* allele was associated with faster cognitive deterioration. Pathological studies indicate that the *APOE ε4* allele is independently associated with more severe Lewy body pathology, regardless of AD pathology levels. This suggests that *APOE ε4* may modify processes favoring Lewy body pathology spread.[19] A recent study that used a real-time quaking-induced conversion (RT-QuIC) assay found that alpha-synuclein seeding

was exacerbated by *APOE ε4* in a small cohort of LBD brains with minimal AD pathology.[20] The impact of the *APOE ε4* allele on alpha-synuclein spread might explain our observation of accelerated progression in carriers. Nevertheless, the *APOE ε4* carriers did not show reduced survival. A possible explanation for this finding is that the main cause of death in DLB may not be directly related to the level of cognitive decline but to the severity of the motor dysfunction. Studies have shown that DLB patients with a higher burden of AD pathology tend to have a higher prevalence of the *APOE ε4* allele. This association was linked to poorer cognitive performance compared with patients with a lower burden of AD pathology.[21-23]

GBA1 mutations are associated with more diffuse neocortical Lewy bodies in PD[24] and DLB,[25] which could explain the increased mortality. However, in DLB, the *GBA1* mutation carriers have also been shown to have less coexistent amyloid pathology,[26] implying that survival in this disease may be mediated primarily by alpha-synuclein pathology, a crucial consideration for designing trials of disease-modifying therapies. Our previous findings revealed that DLB patients with *GBA1* mutations have a more severe disease phenotype[4,5] and that the *APOE ε4* allele acted in a complex interaction so that patients who carried both genetic risk factors had a more severe cognitive and motor involvement at presentation. However, the impact of these two common genetic factors on survival and clinical progression in patients with DLB was unclear. Here we demonstrate a clear impact on survival of *GBA1* mutations and an impact of *APOE ε4* polymorphisms on cognitive progression but not on survival. Further studies will need to examine whether different types of *GBA1* mutations have a differential impact. The main limitation to our study is the limited cognitive follow-up data that were available, potentially resulting in underpowered analysis. The frequency of follow-up may have been influenced by disease severity; however, all patients diagnosed with DLB were offered follow-up at the hospital, which aligns with their typical preference and therefore we believe it is unlikely that this introduced bias into our study. Another limitation is the absence of confirmatory post-mortem pathology, with diagnoses relying on clinical criteria and supporting features. This is likely to have led to an underdiagnosis of cases as previously described.[27] A further limitation is that the cause of death was not available for most patients and that due to the wide variation in the number of clinic follow-up visits and time points only the overall deterioration per year could be calculated. One of the main strengths of the study is the clinical follow-up available for these patients that allowed for high clinical diagnostic accuracy.

Conclusions

In this study we aimed to examine the effect of the two most common genetic factors associated with DLB, *GBA1* mutations and *APOE* polymorphisms, on survival and clinical progression. The effect of various genetic factors on survival is key for assessing prognosis, planning clinical trials, developing disease-modifying treatments, and advancing personalized clinical approaches. The precise effect of these genetic factors and possible interactions with other genetic aspects should be further explored with the use of advanced biomarkers for assessment of different pathologies in vivo.

Acknowledgments: We would like to thank all the patients and their families for taking part in this study.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Evaluation of Cerebrospinal Fluid α-Synuclein Seed Amplification Assay in Progressive Supranuclear Palsy and Corticobasal Syndrome

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Relevant conflicts of interest/financial disclosures: J.L. is an employee of Amprion Inc.

Funding agencies: This work was supported by the PSP Association, CBD Solutions, Medical Research Council UK, and National Institutes of Health Center for Alzheimer's and Related Dementias.

Received: 28 February 2024; **Revised:** 27 August 2024; **Accepted:** 4 September 2024

Published online 20 September 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.30019