GBA mutations increase risk for Lewy body disease with and without Alzheimer disease pathology

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ABSTRACT

Objectives: Mutations in the *GBA* gene occur in 7% of patients with Parkinson disease (PD) and are a well-established susceptibility factor for PD, which is characterized by Lewy body disease (LBD) neuropathologic changes (LBDNCs). We sought to determine whether *GBA* influences risk of dementia with LBDNCs, Alzheimer disease (AD) neuropathologic changes (ADNCs), or both.

Methods: We screened the entire *GBA* coding region for mutations in controls and in subjects with dementia and LBDNCs and no or low levels of ADNCs (pure dementia with Lewy bodies [pDLB]), LBDNCs and high-level ADNCs (LBD-AD), and high-level ADNCs but without LBDNCs (AD).

Results: Among white subjects, pathogenic *GBA* mutations were identified in 6 of 79 pDLB cases (7.6%), 8 of 222 LBD-AD cases (3.6%), 2 of 243 AD cases (0.8%), and 3 of 381 controls (0.8%). Subjects with pDLB and LBD-AD were more likely to carry mutations than controls (pDLB: odds ratio [OR] = 7.6; 95% confidence interval [CI] = 1.8–31.9; $p = 0.006$; LBD-AD: OR = 4.6; CI = 1.2–17.6; $p = 0.025$), but there was no significant difference in frequencies between the AD and control groups (OR = 1.1; CI = 0.2–6.6; $p = 0.92$). There was a highly significant trend test across groups ($\chi^2(1) = 19.3$; $p = 1.1 \times 10^{-5}$), with the likelihood of carrying a *GBA* mutation increasing in the following direction: control/AD < LBD-AD < pDLB.

Conclusions: *GBA* is a susceptibility gene across the LBD spectrum, but not in AD, and appears to convey a higher risk for PD and pDLB than for LBD-AD. PD and pDLB might be more similar to one another in genetic determinants and pathophysiology than either disease is to LBD-AD.

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GLOSSARY

AD = Alzheimer disease; **ADC** = Alzheimer disease center; **ADNCs** = Alzheimer disease neuropathologic changes; **CI** = confidence interval; **DLB** = dementia with Lewy bodies; **LBD** = Lewy body disease; **LBDNCs** = Lewy body disease neuropathologic changes; **OR** = odds ratio; **PD** = Parkinson disease; **PDD** = Parkinson disease with dementia; **pDLB** = pure dementia with Lewy bodies.

Lewy body disease (LBD) represents a continuum of clinicopathologic entities that includes Parkinson disease (PD), PD with dementia (PDD), and dementia with Lewy bodies (DLB). PDD is diagnosed when parkinsonism precedes dementia by at least 12 months, whereas in DLB, dementia occurs before or concurrently with parkinsonism.[1] LBD neuropathologic changes (LBDNCs) include classic histologic inclusions (Lewy bodies) and α-synuclein immunopositive neuronal inclusions and processes (Lewy neurites). However, the pathologic classification of DLB is complex because some cases show LBDNCs with no or low levels of Alzheimer disease (AD) neuropathologic changes (ADNCs), which we refer to as "pure" DLB

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(pDLB), whereas many other cases show LBDNCs with coexistent high levels of ADNCs (LBD-AD). The pathophysiologic relationship among LBD-AD, pDLB, and PDD has not been delineated, and whether there is overlap of genetic risk factors among these disorders remains unclear.

Gaucher disease, the most common lysosomal storage disorder, results from a recessively inherited deficiency of glucocerebrosidase, which is encoded by the *GBA* gene. Heterozygous *GBA* mutation carriers have a 5- to 6-fold increased risk of developing PD.[2] The relationship between *GBA* mutations and DLB is less clear. Several small studies have observed a higher mutation frequency in patients with DLB than in controls,[3,4] but interpretation of these results is limited by methodologic issues. Furthermore, one study reported an increased mutation frequency in patients with AD but without LBDNCs.[5]

To address these issues, we screened for *GBA* in a large sample of subjects with neuropathologically determined AD, LBD-AD, and pDLB, and in controls without dementia.

METHODS

Subjects and clinical evaluation. The study population was composed of 562 autopsied cases with dementia and 391 controls. Subjects with dementia were enrolled in 1 of 7 Alzheimer disease centers (ADCs) (Oregon Health and Science University; Rush University Medical Center; University of California, San Diego; University of Kentucky; University of Pennsylvania; University of Pittsburgh; and University of Washington), in the Rush Memory and Aging Project, or in the Group Health/University of Washington Alzheimer's Disease Patient Registry/Adult Changes in Thought Study. The Group Health/University of Washington Alzheimer's Disease Patient Registry/Adult Changes in Thought Study is a community-based longitudinal study that enrolled individuals aged 65 years or older with dementia[6] or with no dementia[7] from a health maintenance organization in the Seattle area. Expert diagnosticians at the ADCs, Rush Memory and Aging Project, and Group Health/University of Washington Alzheimer's Disease Patient Registry/Adult Changes in Thought Study reviewed subject clinical history, physical examinations, and neuropsychological tests at a consensus diagnosis conference. All individuals included in the dementia group received a clinical diagnosis of "probable AD," "possible AD," or "dementia, type unknown" according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[8] None had a clinical diagnosis of PD.

Controls were elderly adults who were enrolled in longitudinal studies of normal aging as part of the Group Health/University of Washington Alzheimer's Disease Patient Registry/Adult Changes in Thought Study, the Rush Memory and Aging Project, or 1 of 6 ADCs (Oregon Health and Science University; Rush University Medical Center; University of California, San Diego; University of Kentucky; University of Pittsburgh; and University of Washington). All controls were cognitively normal at study entry, as determined by a clinical consensus that considered both clinical history and neuropsychological testing. Controls remained free of cognitive impairment at their last evaluation, as indicated by a detailed clinical assessment (Rush ADC and Rush Memory and Aging Project),[9] a Cognitive Abilities Screening Instrument[10] score >85 (Group Health/University of Washington Alzheimer's Disease Patient Registry/Adult Changes in Thought Study), or a Clinical Dementia Rating score <1 and Mini-Mental State Examination score >26 (all other centers). None of the controls had a clinical diagnosis of a neurodegenerative disease, including PD. The controls consisted of 2 groups, one that underwent autopsy (n = 267) and one in which the subjects were alive at the time the dataset was closed (n = 124). All controls in the autopsied group underwent a clinical evaluation within 3 years of death.

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

Neuropathologic classification. All autopsied cases underwent a standard histologic evaluation using hematoxylin & eosin, modified Bielschowsky, and thioflavine S methods. Immunostaining for LBDNCs was also performed on all autopsied cases using α-synuclein immunohistochemistry with antibody LB509 (1:50 to 1:400; Zymed, San Francisco, CA), as previously described.[11] Cases with questionable LB509 immunoreactivity were evaluated with a second antibody to nitrated α-synuclein (syn 303, 1:1,000).[12] A section from each of the following 5 regions was assessed for LBDNCs: medulla, substantia nigra, amygdala, cingulate gyrus, and frontal cortex. The only exception was that 3 regions (substantia nigra, cingulate gyrus, and frontal cortex) rather than 5 regions were assessed for LBDNCs in cases and controls from Rush University Medical Center. Braak staging[13] for neurofibrillary tangles and Consortium to Establish a Registry for Alzheimer's Disease plaque score[14] were determined using modified Bielschowsky-stained sections, tau immunohistochemistry (AT8, Endogen, 1:250), or both.

All subjects with dementia underwent autopsy and were neuropathologically classified as pDLB (n = 80), LBD-AD (n = 231), or AD (n = 251) based on ADNCs and LBDNCs. AD was defined by the presence of high-level ADNCs (Braak stage IV, V, or VI and a Consortium to Establish a Registry for Alzheimer's Disease plaque score of "moderate" or "frequent") but no LBDNCs. LBD-AD was defined by the presence of both high-level ADNCs and limbic or neocortical stage LBDNCs.[11] pDLB was defined by the presence of limbic or neocortical stage LBDNCs and no or low levels of ADNCs. Note that all cases with ADNCs that did not meet criteria for high level were classified as low level, and we did not include an "intermediate level" in order to maximize statistical power. The autopsied control group showed no evidence of LBDNCs or high-level ADNCs.

Mutational analysis. DNA was extracted from blood or brain tissue using standard methods. Because nearly 300 pathogenic mutations have been reported in patients with Gaucher disease,[15] our screening approach was designed to cover the entire *GBA* coding region. *GBA* was amplified with PCR in 3 fragments of 1.7 to 3.0 kilobases in length using primers that specifically amplify the functional gene but not the nearby pseudogene. All 11 *GBA* exons and intron-exon boundaries were then sequenced using the Applied Biosystems Big-Dye Terminator v3.1 Cycle Sequencing Kit on an ABI PRISM 3130 genetic analyzer (Applied Biosystems, Foster City, CA). Sequence data were base-

Supplemental Data

Table 1 Clinical characteristics of the study population

Group	No.	Male, n (%)[a]	Age, y[b] Mean (SD)	Age, y[b] Range	Age at onset, y[c] Mean (SD)	Age at onset, y[c] Range
Controls	391	163 (41.7)	81.3 (9.1)	54–106	—	—
pDLB	80	62 (77.5)	80.5 (9.3)	57–99	72.8 (11.4)	48–96
LBD-AD	231	102 (44.2)	81.7 (8.6)	60–101	73.7 (10.9)	46–98
AD	251	94 (37.5)	81.7 (8.3)	53–101	73.1 (9.3)	47–100

Abbreviations: AD = dementia with high-level Alzheimer disease neuropathologic changes without Lewy body disease neuropathologic changes; LBD-AD = dementia with Lewy body disease neuropathologic changes and high-level Alzheimer disease neuropathologic changes; pDLB = pure dementia with Lewy bodies (dementia with Lewy body disease neuropathologic changes and no or low-level Alzheimer disease neuropathologic changes).
[a] Overall $\chi^2(3) = 41.6$, $p < 0.001$. Pairwise comparisons that reached significance were pDLB vs LBD-AD $\chi^2(1) = 26.5$, $p < 0.001$; pDLB vs AD $\chi^2(1) = 39.1$, $p < 0.001$; pDLB vs controls $\chi^2(1) = 34.1$, $p < 0.001$.
[b] Age at death for autopsied subjects or age at last clinical assessment for living controls; analysis of variance between groups $F_{3, 949} = 0.49$, $p = 0.69$.
[c] Age at onset of dementia; analysis of variance between groups $F_{2, 543} = 0.28$, $p = 0.76$.

called, aligned, and scanned for variation using Mutation Surveyor (SoftGenetics, State College, PA). A mutation was considered "pathogenic" if it was previously reported in at least one patient with Gaucher disease.[15,16] Fifty-five of the pDLB/LBD-AD cases were previously screened for the 2 most common *GBA* mutations (N370S and L444P); these results have been published elsewhere.[4]

Statistical analysis. Demographic and descriptive information were summarized as means, standard deviations, and ranges for continuous measures and as proportions for discrete variables. Age and age at onset of dementia were compared among groups using analysis of variance. A Pearson χ^2 test was used to evaluate group differences in sex proportions.

The Fisher exact test was used to examine differences in *GBA* mutation frequency among groups. Multinomial logistic regression was used to test for association between *GBA* mutations and each of the 3 disease groups with controls as the reference. A test for a trend in the odds of carrying a mutation by disease group was performed using the score trend test. In this analysis, controls and AD cases were coded as 0, LBD-AD cases were coded as 1, and pDLB cases were coded as 2. All statistical analyses were conducted using STATA version 10 and a p value <0.05 was considered significant.

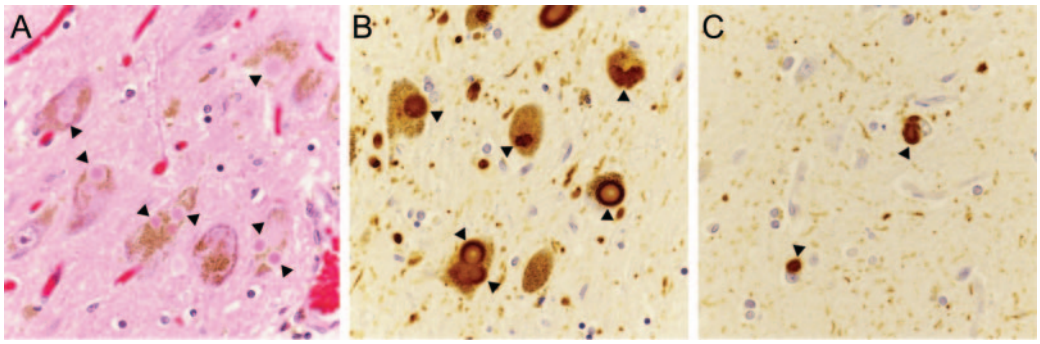
RESULTS The demographic and clinical characteristics of the sample are shown in table 1. A substantially greater proportion of subjects with pDLB were male in comparison to the AD, LBD-AD, and control groups (overall $\chi^2(3) = 41.6$, $p < 0.001$). There were no differences in age or age at onset among groups.

Table 2 lists all *GBA* variants that were observed in the sample within exons or intronic splice sites, including 7 pathogenic mutations, 4 mutations of unknown significance, and 4 nonsynonymous polymorphisms. Note that 2 rare variants, K(−27)R and I(−20)V, were classified as polymorphisms because they have been observed to occur at a frequency of >5% in controls of African [K(−27)R; unpublished data] and Asian [I(−20)V][17] ancestry. Twenty-five subjects were found to carry *GBA* mutations (pathogenic, n = 19; unknown significance, n = 6), and their neuropathologic findings are summarized in table e-1 on the *Neurology*® Web site at www.neurology.org. Eighteen of these mutation carriers displayed LBDNCs (pDLB, n = 7; LBD-AD, n = 11), and 16 of the 18 cases had "neocortical" stage LBDNCs (figure). The remaining 2 cases had "limbic" stage LBDNCs[11] with involvement of the brainstem and cingulate gyrus but sparing of the neocortex. All cases were specifically examined for the pathologic changes previously described in 4 cases of Gaucher disease with parkinsonism and LBDNCs.[18] We observed neither "brainstem-type" Lewy bodies in the hippocampus nor severe neuronal loss and gliosis in the

Table 2 *GBA* variants observed

Variant	No.
Pathogenic mutations	
IVS2 + 1	1
D140H	1
H255Q	1
N370S	11
L444P	1
Rec1 (L444P, A456P, and V460V)	3
R496H	1
Mutations of unknown significance	
R39C	1
R262H	2
E388K	2
H422Y	1
Nonsynonymous polymorphisms	
K(−27)R	2
I(−20)V	1
E326K	31
T369M	13

Figure Lewy body disease neuropathologic changes in subject 18 with an N370S *GBA* mutation



Multiple Lewy bodies by hematoxylin & eosin staining (A, arrowheads) and by α-synuclein immunostaining (B, arrowheads) in the substantia nigra. α-Synuclein immunopositive inclusions (arrowheads) and frequent neurites in the frontal cortex (C). Original magnifications, ×126.

cornu ammonis 2–4 hippocampal subfields or neocortex. However, frequent α-synuclein immunopositive neuronal inclusions were present in the cornu ammonis subregions of all 16 cases with neocortical stage LBDNCs.

The *GBA* mutation frequencies in each group are presented in table 3. Among white subjects, 6 of the 79 cases with pDLB (7.6%) were heterozygous for a pathogenic *GBA* mutation, as were 8 of the 222 cases with LBD-AD (3.6%), 2 of the 243 cases with AD (0.8%), and 3 of the 381 controls (0.8%). There was an overall difference in the frequency of pathogenic *GBA* mutation carriers across groups (Fisher exact test, $p = 0.001$). In comparison to controls, the carrier frequency was elevated in the pDLB ($p = 0.001$) and LBD-AD ($p = 0.022$) groups, but not in the AD group ($p = 1.0$).

In a logistic regression model adjusted for age and sex and limited to white subjects (table 4), pathogenic *GBA* mutations were associated with both pDLB (odds ratio [OR] = 7.6; 95% confidence interval [CI] = 1.8–31.9; $p = 0.006$) and LBD-AD (OR = 4.6; 95% CI = 1.2–17.6; $p = 0.025$), but not AD (OR = 1.1; 95% CI = 0.2–6.6; $p = 0.92$). Inspection of the ORs suggested that individuals with LBD-AD might have a mutation carrier risk intermediate between the pDLB and AD/control groups. We assessed this hypothesis using a trend test. Given that the frequency of *GBA* mutations in controls and AD cases was nearly identical, for the purposes of this test, the controls and AD cases were collapsed into a single group. The results indicated an increased likelihood of carrying a *GBA* mutation across groups in the following direction: control/AD < LBD-AD < pDLB ($\chi^2[1] = 19.3$; $p = 1.1 \times 10^{-5}$).

Table 3 *GBA* mutation frequencies by group[a]

	pDLB	LBD-AD	AD	Controls
Pathogenic mutations, white only	6/79 (7.6)	8/222 (3.6)	2/243 (0.8)	3/381 (0.8)
All mutations, white only	7/79 (8.9)	11/222 (5.0)	3/243 (1.2)	4/381 (1.0)
Pathogenic mutations	6/80 (7.5)	8/231 (3.5)	2/251 (0.8)	3/391 (0.8)
All mutations	7/80 (8.8)	11/231 (4.8)	3/251 (1.2)	4/391 (1.0)

Abbreviations: AD = dementia with high-level Alzheimer disease neuropathologic changes without Lewy body disease neuropathologic changes; LBD-AD = dementia with Lewy body disease neuropathologic changes and high-level Alzheimer disease neuropathologic changes; pDLB = pure dementia with Lewy bodies (dementia with Lewy body disease neuropathologic changes and no or low-level Alzheimer disease neuropathologic changes).
[a] The number of mutation carriers is given relative to all subjects in the group, followed by the percentage of mutation carriers within the group.

DISCUSSION Our results are novel in that they suggest that *GBA* conveys a higher risk for pDLB than for LBD-AD. The observed frequency of pathogenic mutations in the pDLB group (7.6%) was very similar to the 7% frequency reported in a multicenter analysis of 1,883 patients with PD in whom *GBA* was fully sequenced.[2] In contrast to another report,[5] we did not find differences in the proportion of *GBA* mutation carriers between controls and patients with AD.

pDLB and PDD are neuropathologically indistinguishable from one another[19] whereas clinically, pDLB more closely resembles LBD-AD. Also, in contrast to LBD-AD, both pDLB and PDD exhibit a strong male predominance.[20,21] The degree to which genetic factors have a role in shaping the similarities and differences among these 3 clinicopathologic entities is not well understood, in part because very few genetic studies have made a distinction between pDLB and LBD-AD. Our findings address this gap in knowledge and begin to differentiate the "genetic profiles" of PDD, pDLB, and LBD-AD. Taken together with previous work,[2] our data suggest that in terms of the risk conveyed by *GBA* mutations, pDLB and PDD overlap more closely with one another than with LBD-AD. Whether this same pattern will prove to be true for other susceptibility genes remains to be determined.

Five studies[3–5,22,23] have previously investigated the association between *GBA* mutations and DLB,

Table 4 Association of *GBA* mutations with dementia by group

	Pathogenic mutations[a]		All mutations[a]	
Group	OR (95% CI)	*p* Value	OR (95% CI)	*p* Value
Controls	1.0	Reference	1.0	Reference
AD	1.1 (0.2–6.6)	0.92	1.2 (0.3–5.5)	0.81
LBD-AD	4.6 (1.2–17.6)	0.025	4.8 (1.5–15.4)	0.008
pDLB	7.6 (1.8–31.9)	0.006	7.6 (2.1–27.3)	0.002

Abbreviations: AD = dementia with high-level Alzheimer disease neuropathologic changes without Lewy body disease neuropathologic changes; CI = confidence interval; LBD-AD = dementia with Lewy body disease neuropathologic changes and high-level Alzheimer disease neuropathologic changes; OR = odds ratio; pDLB = pure dementia with Lewy bodies (dementia with Lewy body disease neuropathologic changes and no or low-level Alzheimer disease neuropathologic changes).
[a] Restricted to white subjects, and adjusted by age and sex.

and 2 of these studies have reported a significantly higher mutation frequency in the DLB group than in the matched controls.[4,5] The observed DLB mutation carrier frequency varied several-fold across studies, from 27 of 95 cases (28%)[5] to 3 of 57 cases (3.5%).[4] Furthermore, one study[5] reported an increased *GBA* mutation frequency of 10% in 60 cases with a neuropathologic diagnosis of AD and without LBDNCs. There are several factors that might explain these seemingly discrepant findings. Two of the studies lacked sufficient clinical information to exclude all cases with a clinical diagnosis of PD.[5,23] Without making this distinction, one cannot accurately estimate separate mutation frequencies for PD and DLB.[1] Two of the studies did not include a matched control group and instead referenced previously published mutation frequencies in controls.[3,23] All previous studies had more modest sample sizes than the current study and thus only had sufficient power to detect large effects at the expected allele frequencies. One study assessed only the 2 most common pathogenic *GBA* mutations (N370S and L444P) rather than screening the entire coding region.[4] Thus, some other pathogenic mutations were likely missed. In one study, the reported mutation frequency included rare variants of unknown functional significance and low-frequency polymorphisms.[5] Finally, *GBA* mutation frequencies are substantially higher in Ashkenazi Jews,[24] but none of the prior studies reported the proportion of subjects with Ashkenazi Jewish ancestry in the sample.

Our study had several strengths. The sample was large and was well characterized both clinically and neuropathologically. Importantly, all subjects with pDLB and LBD-AD had clinically documented dementia at onset rather than parkinsonism, allowing for exclusion of patients with PDD. We included a matched control group in which all subjects were screened for cognitive impairment and more than half underwent autopsy. All pathologic examinations for LBD were made using the same methods (by J.L., R.H., T.M., J.S., and P.N.). Finally, we comprehensively screened all *GBA* exons rather than selectively genotyping a subset of mutations. Our study also had limitations. Because the majority of subjects included in this clinicopathologic study died before the publication of the clinical criteria for DLB, we were unable to fully apply these criteria retrospectively, in particular the "fluctuating cognition" and "REM sleep behavior disorder" features.[1] Also, as in previous studies, we did not collect information on the presence of Ashkenazi Jewish ancestry in all subjects and thus we cannot entirely exclude the possibility of unrecognized population structure in our dataset.

In a neuropathologic study of 14 patients with Gaucher disease,[18] only the 4 cases that displayed clinical parkinsonism and dementia had LBDNCs. In all cases, the authors noted hippocampal and neocortical gliosis, and they also observed marked neuronal loss in a subset of cases with phenotypically severe type II and III disease. The LBDNCs were unusual in that "brainstem-type" Lewy bodies were seen in the hippocampus. We specifically evaluated the *GBA* mutation carriers identified in our study for these pathologic changes and they were not observed. However, we did observe severe and anatomically diffuse LBDNCs in the majority of *GBA* mutation carriers, including α-synuclein immunopositive inclusions in hippocampal neurons. We suspect that the pathologic differences observed between the Gaucher disease cases with parkinsonism and our patients with pDLB and LBD-AD might be attributable to a gene dosage effect in that the Gaucher disease patients had 2 alleles with reduced or absent function whereas our patients had only 1.

Although findings from this and other case-control studies indicate an association between *GBA* mutations and LBD, the molecular mechanism by which dysfunction of the gene leads to LBDNCs and neurodegeneration has not been fully elucidated. However, recent in vivo and in vitro experiments indicate that *GBA* mutations promote aggregation of α-synuclein[25] and enhance α-synuclein–mediated neurotoxicity,[26] thus providing the first evidence directly linking alteration of glucocerebrosidase function with synucleinopathy.

Despite recent progress on the role of *GBA* in LBD, several critical questions remain to be answered. For example, although *GBA* mutations are a strong risk factor for LBD, most *GBA* carriers remain asymptomatic. Also, for those mutation carriers who do become symptomatic, it is not clear why some present with dementia at onset

(pDLB or LBD-AD) whereas others present with parkinsonism (PD). It is likely that genetic and environmental factors modify the expression of *GBA*-related neurodegeneration. This hypothesis should be tested with large-scale genetic association studies, which incorporate careful clinicopathologic characterization and collection of detailed environmental exposure data. Family-based studies might be particularly fruitful. Although such endeavors will be challenging, the identification of major modifying factors for *GBA*-induced synucleinopathies could substantially accelerate progress in developing improved treatment strategies for LBD.

AUTHOR CONTRIBUTIONS

Dr. Tsuang: study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, and obtaining funding. Dr. Leverenz: study concept and design, acquisition of data, interpretation of data, and drafting of the manuscript. Dr. Lopez: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Hamilton: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Bennett: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Schneider: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Buchman: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Larson: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Crane: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Kaye: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Kramer: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Woltjer: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Kukull: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Nelson: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Jicha: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Neltner: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Galasko: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Masliah: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Dr. Trojanowski: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Schellenberg: critical revision of the manuscript for important intellectual content, interpretation of data, and obtaining funding. Ms. Yearout: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and technical support. Ms. Huston: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and technical support. Ms. Fritts-Penniman: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and technical support. Dr. Mata: critical revision of the manuscript for important intellectual content, acquisition of data, and interpretation of data. Ms. Wan: statistical analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Edwards: statistical analysis, interpretation of data, and critical revision of the manuscript for important intellectual content. Dr. Montine: critical revision of the manuscript for important intellectual content, acquisition of data, interpretation of data, and obtaining funding. Dr. Zabetian: study concept and design, acquisition of data, interpretation of data, drafting of the manuscript, and obtaining funding.

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DISCLOSURE

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