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LRRK2 variation and dementia with Lewy bodies

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Abstract

Introduction—The leucine-rich repeat kinase 2 (*LRRK2*) gene contains several variants that cause Parkinson's disease (PD) and others that modify PD risk. However, little is known about the role of *LRRK2* in dementia with Lewy bodies (DLB). Aims of this study were to screen DLB patients for pathogenic *LRRK2* variants and to evaluate associations between common *LRRK2* variants and risk of DLB.

Methods—417 clinical DLB patients and 1,790 controls were included in the primary analysis. Additionally, 355 Lewy body disease patients assessed as having a high likelihood of clinical DLB based on neuropathological findings were included in secondary analysis. Seven pathogenic *LRRK2* variants were assessed in patients, while 17 common *LRRK2* exonic variants and 1 GWAS-nominated common *LRRK2* PD-risk variant were evaluated for association with DLB.

Results—We identified carriers of 2 different pathogenic *LRRK2* variants. One clinical DLB patient was a p.G2019S carrier, while in the pathological high likelihood DLB series there was one carrier of the p.R1441C mutation. However, examination of clinical records revealed the p.R1441C carrier to have PD with dementia. Evaluation of common variants did not reveal any associations with DLB risk after multiple testing adjustment. However, a non-significant trend similar to that previously reported for PD was observed for the protective p.N551K-R1398H-K1423K haplotype in the clinical DLB series (OR: 0.76, P=0.061).

Conclusion—*LRRK2* does not appear to play a major role in DLB, however further study of p.G2019S and the p.N551K-R1398H-K1423K haplotype is warranted to better understand their involvement in determining DLB risk.

Keywords

dementia with Lewy bodies; genetics; *LRRK2*; Parkinson's disease

INTRODUCTION

Dementia with Lewy bodies (DLB) is one of the most common types of dementia in the elderly population, and has clinical and neuropathological similarities with both Alzheimer's disease (AD) and Parkinson's disease (PD).[1] DLB is characterized clinically by

progressive dementia, parkinsonism, visual hallucinations, fluctuations in cognition, and REM sleep behavior disorder.[2] Neuropathologically, DLB is classified as an α-synucleinopathy along with PD and PD with dementia (PDD) owing to the typical widespread presence of cortical Lewy bodies, and this is often observed along with pathological features of AD such as neurofibrillary tangles (NFTs) and senile plaques.[2] Genetic causes of DLB are not well understood, however recent studies have implicated genes involved in both AD and PD. Specifically, strong associations with DLB have been observed for the apolipoprotein E (*APOE*) ε4 allele which is a major risk factor for AD, and also for variants in the glucocerebrosidase (*GBA*) and α-synuclein (*SNCA*) genes, which are both well-known risk factors for PD.[3-5]

The common clinical and neuropathological features between DLB and PD and the identification of shared genetic risk factors for these two diseases suggests that other PD-genes may be promising candidates for study in relation to risk of DLB. The leucine-rich repeat kinase 2 (*LRRK2*) gene has a well-known role in PD, containing both disease-causing mutations such as p.G2019S and p.R1441C, as well as common disease-risk-modifying variants including p.M1646T in Caucasians, p.G2385R and p.R1628P in Asians, and a protective p.N551K-R1398H-K1423K haplotype in both ethnic groups.[6-10] However, *LRRK2* has not been well-studied in the context of DLB. Specifically, the association between common *LRRK2* variation and DLB risk has not been systematically examined to date, and assessment of pathogenic *LRRK2* mutations has been limited to a few relatively small case series' and one familial study.[11-14] In this study, we utilized a series of more than 700 patients with either clinically diagnosed DLB or neuropathologically-assessed Lewy body disease with a high likelihood of DLB in order to estimate the frequencies of pathogenic *LRRK2* variants and also to evaluate associations between common *LRRK2* variants and risk of DLB.

METHODS

Study subjects

Included in the primary analysis of this study were 417 clinical DLB patients and 1790 controls. The clinical DLB patients were seen at the Mayo Clinic in either Jacksonville, FL (N=152) or Rochester, MN (N=265) between 1987 and 2014, and DLB diagnosis (384 probable DLB, 33 possible DLB) was made in accordance with published criteria.[2] Clinical DLB patients collected at both Mayo sites were part of NIH-funded studies on aging and dementia (Alzheimer's Disease Research Center or Mayo Clinic Study of Aging) and the Mayo Clinic Udall Center of Excellence in Parkinson's Disease Research.. Controls were individuals free of neurological disease seen at the Mayo Clinic in Jacksonville, FL. The clinical DLB patients and controls was considered to be our primary patient-control series owing to a clinical diagnosis of DLB that was made based on observed patient symptoms.

In secondary analysis, we also included 355 autopsy-confirmed Lewy body disease patients who were assessed as high likelihood DLB according to the criteria of the third report of the DLB consortium (CDLB).[2] Clinical information was generally unavailable for these 355 patients; diagnosis was made purely based on neuropathological findings. This secondary

series was comprised of all cases that were received at the Mayo Clinic Jacksonville brain bank for neurodegenerative disorders between 1990 and 2013 that satisfied our inclusion criteria. We did not include amygdala predominant or incidental Lewy body disease cases since these cannot be used to estimate clinical likelihood of DLB according to CDLB criteria.[2] We also excluded LBD cases that had significant coexisting non-AD pathology (i.e. progressive supranuclear palsy, corticobasal degeneration, Pick's disease, or multiple system atrophy). Finally, since the focus of this study was on DLB, we excluded cases that were assessed as either low or intermediate likelihood of clinical DLB by CDLB criteria [2] from our analysis, including only those cases who were assessed as high likelihood DLB. According to CDLB criteria, LBD cases are assigned a likelihood (low, intermediate, or high) of clinical DLB according to severity of LB pathology by the staging scheme of Kosaka and colleagues [15] and also severity of AD pathology as measured by Braak neurofibrillary tangle stage [16]; patients with a high likelihood of clinical DLB are those with a Braak stage of 0-II and either transitional or diffuse Lewy body disease, or Braak stage III-IV and diffuse Lewy body disease.[2] It should be further highlighted that the pathological high likelihood DLB series is not defined by clinical symptoms; although a clinical diagnosis of AD is relatively unlikely in this group [17], neuropathological features are similar for DLB and those of advanced PD and PDD.[18]

Forty-seven patients were in both the clinical DLB series and the pathological high likelihood DLB series. Therefore, this study examined a total of 725 different patients who were assessed either clinically as DLB or pathologically as high likelihood DLB. All subjects were unrelated Caucasians, and individuals with a known *SNCA* mutation were excluded. This study was approved by the Mayo Clinic institutional review board. All clinical DLB patients and controls provided informed consent. For high likelihood DLB cases, informed consent was provided by the legal next of kin. Age and gender are summarized in Table 1 for each disease group.

Neuropathologic assessment

Neuropathologic methods have previously been described in detail.[19] Briefly, neuroanatomical sampling and thioflavin-S fluorescence microscopy were performed using the sampling design of Terry and colleagues.[20] Formalin-fixed, paraffin-embedded tissue from the limbic region and cortical region were cut at 5 μm thickness and mounted on glass slides. NFTs were evaluated using thioflavin-S fluorescent microscopy. Both mature (intracellular) and ghost (extracellular) NFTs were quantified, and used to assign a Braak NFT stage.[16] LB pathology was assessed using an α-synuclein antibody (NACP, 1:3000 rabbit polyclonal, Mayo Clinic antibody) and was processed using the DAKO Autostainer (DAKO Auto Machine Corporation, Carpinteria, CA) with DAKO Envision+ HRP System.

Genetic analysis

DNA for the clinical DLB and control subjects was extracted from blood using the Autogen Flex Star (Holliston, MA) and DNA for the high DLB likelihood Lewy body disease patients was extracted from frozen brain tissue using the Autogen 245T (Holliston, MA). For common variants, all 17 *LRRK2* exonic variants that were previously observed with a minor allele frequency of 0.5% or greater in a large study by the Genetic Epidemiology of

Parkinson's Disease Consortium (GEO-PD) [7] were selected for inclusion, as well as the rs76904798 variant, located on chromosome 12, that was recently identified as a risk factor for PD in a meta-analysis of genome-wide association studies.[21] Additionally, we screened both the clinical DLB and pathological high likelihood DLB series for the 7 definite pathogenic *LRRK2* mutations that have been identified to date (p.N1437H, p.R1441C, p.R1441G, p.R1441H, p.Y1699C, p.G2019S, and p.I2020T).

The 5 variants in exons 34 and 37 of *LRRK2* were genotyped using bidirectional Sanger sequencing on an ABI 3730XL DNA sequencer (Life Technologies, Carlsbad, CA, USA). The remaining exonic *LRRK2* variants were genotyped using Sequenom Mass Array iPlex Gold chemistry and analyzed using Typer 4.0 (Sequenom, San Diego, CA, USA). The rs76904798 variant was genotyped using ABI SNP Genotyping Taqman assay and genetic analysis was completed using SDS 2.2.2 software (Life Technologies, Carlsbad, CA, USA). All pathogenic mutations were confirmed using bidirectional Sanger sequencing. All genotype call rates were >95% and there was no evidence of a departure from Hardy-Weinberg equilibrium in controls for any variant (all P>0.05). Linkage disequilibrium in controls is summarized in Supplementary Tables 1a and 1b for common variants.

Statistical analysis

After exclusion of carriers of pathogenic variants, associations with disease (clinical DLB vs. controls and pathological high likelihood DLB vs. controls separately) for each common *LRRK2* variant were evaluated using logistic regression models that were adjusted for age and gender. Odds ratios (ORs) and 95% CIs were estimated. *LRRK2* variants were examined under a dominant model (i.e. presence vs. absence of the minor allele) due to the small number of rare homozygotes for many of the variants. We also combined the clinical DLB series and pathological high likelihood DLB cases into one overall disease group in logistic regression disease association analysis; for the 47 cases who were in both series, these were only considered once in combined analysis. Haplotype analysis was performed using score tests for association with the aforementioned model adjustments, and where haplotypes with a frequency of less than 1% were not considered. In order to adjust for multiple testing in single-variant association analysis, we utilized a single-step minP permutation correction separately for each disease outcome; after this adjustment, p-values ≤ 0.0037 (clinical DLB vs. controls), ≤ 0.0041 (high likelihood DLB vs. controls), and ≤ 0.0040 (combined disease group vs. controls) were considered as statistically significant. All statistical analyses were performed using R Statistical Software (version 2.14.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Pathogenic *LRRK2* mutations in DLB

We identified one LRRK2 p.G2019S carrier (0.2%) who was part of the clinical DLB series. This patient was a 76-year-old, functionally independent man who initially presented with concurrent onset of REM-sleep behavior disorder, decline in attention and word-finding ability, and right-sided resting tremor. An initial neuropsychological examination was significant for mild impairment in divided attention and poor learning and retrieval, but no

rapid forgetting. Two years after symptom onset, a second neuropsychological evaluation showed interval decline in processing speed, basic and divided attention, naming, and visual problem-solving skill, with stable and normal memory retention. Family members reported further cognitive difficulties characterized by daily fluctuations and a decline in functional independence. He experienced a few isolated instances of fully-formed visual hallucinations that did not reoccur. Neurological examination that year showed worsening of his rest tremor and onset of rigidity, hypomimia, micrographia, and bradykinesia. The patient was diagnosed with probable DLB based on CDLB criteria.[2] He began treatment with galantamine, which led to temporary improvement in his attention and fluctuations. During his final clinical exam six years after symptom onset, his parkinsonism and cognitive status had declined further and he was no longer able to perform basic functional activities. This patient's *APOE* genotype was ε3/ε4 and he had no known family history of neurodegenerative disease.

There was also one carrier (0.3%) of the LRRK2 p.R1441C mutation in the secondary high likelihood DLB series. This patient is a member of Family D (Western Nebraska, III-20) in which pathogenic *LRRK2* mutations were first identified in PD.[22] Clinical records available for this patient show a clinical diagnosis of probable PD; characteristics of this patient have been documented previously.[22,23] Briefly, this was a female patient who was diagnosed with PD at age 68. After her initial symptom of tremor, she eventually developed classic features of PD including bradykinesia, rigidity, and postural instability. A positive response to levodopa therapy was observed. She developed cognitive deficits approximately 1-2 years prior to her death at age 89, and her diagnosis was updated to PDD. This patient had diffuse Lewy body disease, was Braak stage III, and her *APOE* genotype was ε3/ε3.

No additional p.G2019S or p.R1441C mutations were observed. Additionally, there were no carriers of the p.N1437H, p.R1441G, p.R1441H, p.Y1699C, or p.I2020T mutations in either the clinical DLB series or the pathological high likelihood DLB series.

Associations between common *LRRK2* variants and risk of DLB

An evaluation of the associations between the 18 common *LRRK2* variants and DLB risk is displayed in Table 2. None of the *LRRK2* variants were significantly associated with risk of clinical DLB or pathological high likelihood DLB after adjustment for multiple testing. A non-significant trend was observed for p.N551K in the clinical DLB series (OR: 0.73, P=0.067) and also the combined series (OR: 0.78, P=0.062). The p.M1646T PD-risk variant was nominally associated with risk of high likelihood DLB (OR: 1.92, P=0.030), but this trend was not observed in the clinical DLB series or combined series. Genotype counts and frequencies for each variant are shown in Supplementary Tables 2a-2c.

The aforementioned p.N551K variant that showed a trend toward association with risk of clinical DLB is part of a 3-variant p.N551K-R1398H-K1423K haplotype that has been shown to be protective for PD.[7,10] When evaluating the association between this 3-variant haplotype and risk of disease, we again observed a non-significant trend in the clinical DLB series (OR: 0.76, P=0.061), but not in the pathological high likelihood DLB series (OR: 0.88, P=0.64) or the combined series (OR: 0.81, P=0.23).

DISCUSSION

LRRK2 mutations are the most common genetic cause of PD that have been identified thus far, however little is known about its role in DLB. To date, there have been no pathogenic *LRRK2* mutations that have been reported in clinically diagnosed DLB patients, and associations with DLB for common *LRRK2* variants have been only minimally assessed. In our study of 417 clinically diagnosed DLB patients, we identified one clinical DLB p.G2019S mutation carrier, and we also observed a non-significant trend toward association between the p.N551K-R1398H-K1423K haplotype and DLB risk that is similar to what has been observed in much larger studies of PD. We also observed a carrier of the p.R1441C mutation in our secondary high likelihood DLB series, however on review this patient had a clinical diagnosis of PDD.

LRRK2 pathogenic mutation carriers with PD have generally displayed clinical characteristics similar to that of idiopathic PD, however neuropathological findings have varied considerably [24], suggesting that these mutations may cause a wider range of phenotypes other than just PD. Indeed, *LRRK2* has been studied in a wide range of neurodegenerative disorders, with a small number of pathogenic mutation carriers identified in progressive supranuclear palsy (p.R1441H) [25], corticobasal syndrome (p.G2019S) [26], frontotemporal lobar degeneration with ubiquitinated neuronal cytoplasmic inclusions (p.G2019S) [27], and dementia and AD (p.Y1699C, p.G2019S).[22,28] To our knowledge this is the first report of a p.G2019S mutation carrier with a clinical diagnosis of DLB. This mutation has been absent in previous studies of DLB patients, though sample sizes have been small.[11-13] However, it is important to acknowledge that similar non-DLB phenotypes have been previously noted. Specifically, the distinction between DLB and PDD is a subject of much debate given the similar clinical and neuropathological features of these two diseases, and indeed carriers of pathogenic *LRRK2* mutations in PDD patients have been reported.[13,28] Of note, a study of PD patients by Srivatsal et al. observed a significantly lower frequency of dementia in pathogenic *LRRK2* mutation carriers (most p.G2019S) compared to non-carriers [29], which is in line with our findings where LRRK2 p.G2019S mutation was observed less frequently in clinical DLB patients compared to previous reports of PD in Caucasian populations [7]. Also of potential importance is the fact that p.G2019S carrier in our clinical DLB series had one copy of the *APOE* ε4 allele, raising the possibility that the presence of this strong AD risk factor could have also influenced the patient's phenotype. Nevertheless, the identification of a clinically diagnosed DLB patient with the p.G2019S mutation suggests that further screening is warranted.

The only previous study of the association between common *LRRK2* variants and DLB was performed by Bras et al., where variants within 500 kb of the rs76904798 variant included in our study were assessed in a series of 788 DLB patients and 2624 controls.[4] The strongest association that was identified in *LRRK2* occurred for rs11175645 (an intronic variant not included in our study) with an OR of 0.81 (P=0.035), however this did not approach statistical significance after multiple testing adjustment ($P \leq 3.7 \times 10^{-5}$). Similarly, we did not observe any significant associations between the 17 common *LRRK2* exonic variants and the GWAS SNP examined in our study and risk of DLB when adjusting for the number of statistical tests that were performed. However, although our sample size is large for a

study of DLB, it is relatively small for a genetic association study, and therefore the possibility of a false-negative association is important to consider. With that in mind, it is worth reporting several noteworthy findings that are similar to those that have been previously observed in PD and should therefore be further examined in larger DLB series. Specifically, although the non-significant trend was only observed in the clinical DLB series, the magnitude of the protective association for the p.N551K-R1398H-K1423K haplotype in the clinical DLB series and combined series is similar to what has been previously observed for PD in a Caucasian population (OR: 0.86).[7] Additionally, we observed a nominally significant association between p.M1646T and risk of high likelihood DLB, which is stronger than previous reports in PD (OR: 1.43).[7]

Several caveats of our study should be noted. The high likelihood DLB series is pathologically defined according to likelihood of clinical DLB. Therefore, in addition to patients with DLB, it without question contains some patients with advanced PD and PDD [18], as we observed for the p.R1441C carrier for whom clinical records were available and revealed a diagnosis of PDD. Accordingly, we considered this series to be secondary, and results involving it should be interpreted with this limitation in mind. Also, although all clinical DLB patients were diagnosed as probable DLB, the clinical DLB series lacks pathologic confirmation and therefore may contain other pathologies clinically manifesting as DLB. Finally, as previously referred to, the sample size of our study is relatively small for a genetic study, and therefore larger studies are needed to better understand the how rare and common *LRRK2* variants may alter risk of DLB.

In conclusion, our results suggest that *LRRK2* likely does not play a major role in DLB. However, our frequency and association estimates are relatively imprecise in this small sample, contrasting with studies of *LRRK2* in PD which have involved thousands of patients. Taking that into account, the identification of a clinical DLB patient with the LRRK2 p.G2019S mutation, combined with the non-significant trend toward association of the p.N551K-R1398H-K1423K haplotype in the clinical DLB series, suggests that this PD-gene could have a limited role in susceptibility to DLB and should be studied further in larger series of DLB patients. Pathogenic mutations in *LRRK2* occur relatively rarely, with estimated frequencies for the most common p.G2019S mutation of approximately 1-2% in sporadic PD and 4-5% in familial PD in populations of European descent.[30] Consequently, large meta-analytical studies will likely be needed in order to adequately assess the impact of these mutations on DLB risk. However, the frequency of LRRK2 p.G2019S in PD increases to as high as 40% in North African Arabs and Ashkenazi Jews [30], and therefore studies of DLB patients from these populations has potential to offer important insight into the role of *LRRK2* in this less-studied α-synucleinopathy without the need for extremely large sample sizes that can be difficult to achieve.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We studied 417 DLB patients and 1,790 controls in our primary analysis.
- 7 pathogenic *LRRK2* variants and 18 common *LRRK2* variants were assessed.
- We identified 1 DLB patient who was a carrier of the LRRK2 p.G2019S mutation.
- The p.N551K-R1398H-K1423K haplotype showed a non-significant trend toward a protective association with DLB risk.
- These findings suggest that *LRRK2* variation may play a limited role in susceptibility to DLB.

Table 1

Subject characteristics

Group	N	Median (range) age[1]	No. (%) male
Controls	1790	79 (45, 99)	897 (50.1%)
Clinical DLB patients	417	73 (50, 100)	313 (75.1%)
Pathological high likelihood DLB patients	355	78 (50, 103)	224 (63.1%)

[1]Age at last follow up is given for controls, age at DLB onset is given for clinical DLB patients, and age at death is given for pathological high likelihood DLB patients. DLB=dementia with Lewy bodies.

Table 2

Association of common *LRRK2* variants with risk of clinical DLB and pathological high likelihood DLB

			Clinical DLB patients vs. controls				Pathological high likelihood DLB patients vs. controls			Combined disease group vs. controls		
Variant	**Amino acid**	**MA**	**MAF in patients (N=416)**	**MAF in controls (N=1790)**	**OR (95% CI)**	**P-value**	**MAF in patients (N=354)**	**OR (95% CI)**	**P-value**	**MAF in patients (N=723)**	**OR (95% CI)**	**P-value**
rs10878245	L153L	T	39.1%	38.2%	1.04 (0.83, 1.30)	0.74	40.7%	1.11 (0.87, 1.41)	0.40	40.2%	1.09 (0.91, 1.30)	0.37
rs7308720	N551K	G	5.5%	7.6%	0.73 (0.52, 1.03)	0.067	6.5%	0.85 (0.60, 1.19)	0.34	6.0%	0.78 (0.06, 1.02)	0.062
rs10878307	I723V	G	8.3%	7.7%	1.07 (0.79, 1.45)	0.66	8.2%	1.01 (0.74, 1.39)	0.94	8.4%	1.07 (0.84, 1.36)	0.61
rs7966550	L953L	C	11.4%	12.6%	0.89 (0.68, 1.16)	0.40	12.5%	1.03 (0.79, 1.35)	0.83	11.9%	0.95 (0.77, 1.17)	0.64
rs7133914	R1398H	A	5.7%	7.4%	0.78 (0.55, 1.09)	0.14	6.9%	0.94 (0.68, 1.32)	0.73	6.2%	0.85 (0.65, 1.10)	0.22
rs11175964	K1423K	A	5.5%	7.3%	0.78 (0.55, 1.09)	0.15	6.6%	0.91 (0.65, 1.27)	0.58	6.0%	0.83 (0.64, 1.08)	0.17
rs35507033	R1514Q	A	1.2%	0.8%	1.72 (0.81, 3.65)	0.16	0.7%	0.91 (0.34, 2.39)	0.84	1.0%	1.29 (0.67, 2.50)	0.45
rs33958906	P1542S	T	2.5%	2.8%	0.92 (0.56, 1.50)	0.73	3.0%	1.11 (0.68, 1.81)	0.67	2.8%	1.05 (0.72, 1.54)	0.80
rs1427263	G1624G	C	35.0%	35.1%	1.07 (0.86, 1.34)	0.54	35.6%	0.96 (0.76, 1.21)	0.74	35.1%	0.99 (0.83, 1.19)	0.93
rs11176013	K1637K	A	45.3%	45.1%	1.07 (0.84, 1.36)	0.59	45.2%	1.00 (0.78, 1.28)	0.99	45.2%	1.02 (0.84, 1.24)	0.82
rs35303786	M1646T	C	1.1%	1.3%	0.88 (0.42, 1.84)	0.73	2.3%	1.92 (1.07, 3.45)	0.030	1.6%	1.32 (0.78, 2.21)	0.30
rs11564148	S1647T	A	31.3%	30.4%	1.10 (0.88, 1.36)	0.42	30.1%	1.08 (0.86, 1.36)	0.50	30.4%	1.08 (0.90, 1.28)	0.42
rs10878371	G1819G	T	45.4%	45.1%	1.07 (0.84, 1.36)	0.60	45.1%	1.00 (0.77, 1.28)	0.97	45.2%	1.02 (0.84, 1.24)	0.84
rs33995883	N2081D	G	2.0%	1.9%	1.04 (0.59, 1.82)	0.89	2.5%	1.31 (0.76, 2.28)	0.33	2.3%	1.17 (0.75, 1.81)	0.49
rs10878405	E2108E	A	31.6%	31.0%	1.05 (0.84, 1.31)	0.66	30.9%	1.03 (0.82, 1.29)	0.83	31.0%	1.02 (0.86, 1.22)	0.80
rs33962975	G2385G	G	14.8%	14.1%	0.97 (0.76, 1.25)	0.82	13.6%	0.94 (0.72, 1.23)	0.65	14.3%	0.96 (0.79, 1.18)	0.70
rs3761863	M2397T	T	34.4%	34.5%	1.08 (0.86, 1.35)	0.50	35.7%	1.08 (0.86, 1.37)	0.51	35.0%	1.07 (0.89, 1.27)	0.48
rs76904798	N/A[1]	T	13.7%	14.0%	0.91 (0.71, 1.17)	0.44	13.3%	0.93 (0.71, 1.22)	0.61	13.8%	0.96 (0.78, 1.17)	0.66

MA=minor allele; MAF=minor allele frequency; OR=odds ratio; CI=confidence interval. ORs, 95% CIs, and p-values result from logistic regression models adjusted for age (age at DLB onset in clinical DLB patients, age at death in pathological high likelihood DLB patients, and age at last follow-up in controls) and gender. Each *LRRK2* variant was examined under a dominant model, and therefore ORs correspond to presence of the minor allele. After applying a single-step minP permutation adjustment for multiple testing, p-values ≤ 0.0037 (clinical DLB vs. controls), ≤ 0.0041 (pathological high likelihood DLB vs. controls), and ≤0.0040 (combined disease group vs. controls) were considered as statistically significant.

[1] rs76904798 is not an exonic variant.