Systematic review of genetic association studies in people with Lewy body dementia

Hazel Sanghvi 1  |  Ricky Singh 1  |  Hamilton Morrin 1  |  Anto P. Rajkumar 2,3

1 GKT School of Medical Education, King’s College London, London, UK
2 Department of Old Age Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK
3 Institute of Mental Health, Division of Psychiatry and Applied Psychology, University of Nottingham, Nottingham, UK

Correspondence
Anto P. Rajkumar, MD, DNB, MRCPsych, PhD, MD, Clinical Associate Professor, Department of Old Age Psychiatry, Institute of Mental Health, Division of Psychiatry and Applied Psychology, University of Nottingham, Nottingham NG7 2TU, UK.
Email: anto.rajamani@nottingham.ac.uk

Objectives: Lewy body dementia (LBD) causes more morbidity, disability, and earlier mortality than Alzheimer disease. Molecular mechanisms underlying neurodegeneration in LBD are poorly understood. We aimed to do a systematic review of all genetic association studies that investigated people with LBD for improving our understanding of LBD molecular genetics and for facilitating discovery of novel biomarkers and therapeutic targets for LBD.

Methods: We systematically reviewed five online databases (PROSPERO protocol: CRD42018087114) and completed the quality assessment using the quality of genetic association studies tool.

Results: Eight thousand five hundred twenty-one articles were screened, and 75 articles were eligible to be included. Genetic associations of LBD with APOE, GBA, and SNCA variants have been replicated by two or more good quality studies. Our meta-analyses confirmed that APOEε4 is significantly associated with dementia with Lewy bodies (pooled odds ratio [POR] = 2.70; 95% CI, 2.37-3.07; P < .001) and Parkinson’s disease dementia (POR = 1.60; 95% CI, 1.21-2.11; P = .001). Other reported genetic associations that need further replication include variants in A2M, BCHE-K, BCL7C, CHRFAM7A, CNTN1, ESR1, GABRB3, MAPT, mitochondrial DNA (mtDNA) haplogroup H, NOS2A, PSEN1, SCARB2, TFAM, TREM2, and UCHL1.

Conclusions: The reported genetic associations and their potential interactions indicate the importance of α-synuclein, amyloid, and tau pathology, autophagy lysosomal pathway, ubiquitin proteasome system, oxidative stress, and mitochondrial dysfunction in LBD. There is a need for larger genome-wide association study (GWAS) for identifying more LBD-associated genes. Future hypothesis-driven studies should aim to replicate reported genetic associations of LBD and to explore their functional implications.

KEYWORDS
apolipoprotein E, genetic association studies, genetics, Lewy body dementia, Parkinson disease

1 INTRODUCTION

Lewy body dementia (LBD) is the second most common neurodegenerative dementia after the dementia in Alzheimer disease (AD), and it accounts for 15% to 30% of all neurodegenerative dementias.1,2 LBD composes of two overlapping clinical syndromes, dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD).2 LBD is associated with increased mortality,3 earlier nursing home admissions, higher risk of falls, poorer quality of life, higher costs,4 and more caregivers’ burden than AD. Overall, LBD carries a poorer...
prognosis than AD, with accelerated cognitive decline and a greater negative impact on quality of life. The search for disease modifying drugs and reliable peripheral biomarkers for LBD is still ongoing.

Despite the public health importance of LBD, very little is known about the molecular pathology underlying neurodegeneration in LBD. Systematic research on the genetics of LBD remains sparse. While most cases of LBD appear sporadic, several studies have reported familial aggregation of LBD and its core features such as visual hallucinations and cognitive fluctuations. Siblings of probands with DLB have been reported to have significantly higher risk of developing DLB than the siblings of probands with AD. Research in these families has supported a role for genes implicated in both AD (APP, PSEN1, PSEN2, PGRN, and PRNP) and Parkinson disease (PD) (SNCA, SNCB, LRRK2, and GBA) with the development of DLB and PDD. However, autosomal dominant inheritance mutations in SNCA and LRRK2 in people with LBD have been reported. PDD has been associated with variants in PARK1, PARK4, GBA, MAPT, LRRK2, and APOE. While the variants in APOE and GBA have been associated with both DLB and PDD, the associations are stronger for DLB over PDD. Most of the candidate gene association studies that investigated the genetics of LBD were small, and their findings were poorly replicated. The first genome-wide association study (GWAS) investigating DLB was published in January 2018. It estimated 36% heritability of DLB, and it confirmed the associations between DLB and variants in APOE, SNCA, and GBA. Further imputation and genome-wide complex trait analysis of the GWAS data have updated the heritability of DLB as 59.9% and have indicated that the genetic risk factors for DLB are likely to be independent from known AD and PD risk variants.

Identification of genetic variants associated with LBD will improve our understanding of neurodegeneration in LBD and its molecular pathogenesis. Identifying a unique genetic profile will help in distinguishing LBD from AD and defining the nosological boundaries between DLB and PDD. This can facilitate discovery of reliable diagnostic biomarkers for LBD and of novel targets for future therapeutic approaches. In order to provide a comprehensive summary of all available evidence on the genetic associations of LBD, we aimed to conduct the first systematic review of all genetic association studies that investigated people with LBD.

2 | METHODS

2.1 | Study design

The protocol for this systematic review has been registered in the international prospective register of systematic reviews (PROSPERO protocol CRD42018087114; available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?id=CRD42018087114).

2.2 | Search strategy

We systematically searched the following online databases: MEDLINE/PubMed (since 1946), EMBASE (since 1974), PsycINFO (since 1806), CINAHL Complete (since 1937), OpenGrey, and Bielefeld Academic Search Engine (BASE) (since 2004). The search strategy included combinations of population search terms and exposure search terms. The population search terms were (“Lewy” OR “Parkinson**”) AND “Dementia.” The exposure search terms included (“Gene**” AND (“association**” OR “variant**” OR “polymorphism**”) OR (Genome AND association)) OR “mutation**” OR “SNP” OR “CNV” OR “copy number variant**” OR “rare variant**” OR “microsatellite**” OR “chromosome**.” The searches were limited to 3 February 2018 and to English. Reference lists of the studies included in the review were explored for identifying other potentially eligible studies.

2.3 | Eligibility criteria

We included all genetic association studies that satisfied the following inclusion criteria: (a) they were human studies. Studies on animals or cell lines were not included; (b) they presented original research data; (c) participants in at least one study group were clinically diagnosed to have DLB or PDD or LBD; (d) there was a control group in which LBD was clinically ruled out. The controls were either older people without cognitive impairment or those with other neurodegenerative disorders excluding LBD. We excluded studies that were not published in English.

2.4 | Study selection

We screened for all eligible candidate gene association studies and GWAS investigating the genetic associations of LBD. We merged our search results and removed duplicates. We excluded the abstracts that did not mention investigating the genetic association(s) between LBD and one or more genetic variants. We attempted retrieving full texts of all potentially eligible abstracts, and a three-member review team assessed the eligibility of the full-text papers. When a conference abstract was not accompanied by its full presentation, we requested further details from the corresponding author if the contact information was provided. If the corresponding author did not respond to our request within 14 days, we excluded that abstract.

Key Points
- Genetic associations between DLB and genetic variants in APOE, GBA, and SNCA have been replicated by at least two good quality studies.
- Genetic associations of PDD with variants in APOE and GBA have been replicated.
- Our meta-analyses confirm the associations of APOE ε4 with DLB and PDD.
2.5 | Data extraction

We extracted the following data: (a) population characteristics including their mean age and ethnicity, (b) sample size in each study group, (c) definition of the phenotype, (d) investigated genetic variant(s), (e) genotyping method, (f) study findings with effect size and P values, (g) statistical correction for multiple testing, and (h) statistical analyses addressing the effects of potential confounders.

2.6 | Quality assessment

We assessed the quality of eligible studies using the quality of genetic association studies tool (Q-Genie). The Q-Genie assesses the following 11 dimensions: (a) the rationale for study, (b) selection and definition of outcome, (c) selection and comparability of comparison groups, (d) technical classification of the genetic variant(s), (e) non-technical classification of the genetic variant(s), (f) other sources of bias, (g) sample size and power, (h) a priori planning of statistical analyses, (i) statistical methods and control for confounding, (j) tests of assumptions and inferences for the genetic analyses, and (k) appropriate interpretation of the study results. Each dimension is scored on a scale from 1 (poor) to 7 (excellent). For studies with control group, Q-Genie total scores less than or equal to 35 indicate good quality, and total scores more than 45 indicate moderate quality. The reliability and validity of the Q-Genie tool has already been demonstrated. We assessed the interrater reliability of the Q-genie scores between the three members of the review team using the STATA 15.1 software (StataCorp LLC, TX, USA). The two-way mixed-effects intraclass correlation coefficient (ICC) analyses confirmed moderate reliability (ICC = 0.70).

2.7 | Data reporting

When the studies included in this systematic review have reported the dbSNP identifiers (rs IDs) of their investigated genetic variants, we have extracted the information and have reported them in this review. When the included studies have not reported the dbSNP identifiers, we searched the dbSNP database (https://www.ncbi.nlm.nih.gov/snp) with the reported names of the variants. When our search could not establish a unique dbSNP identifier, we have reported the variant name as it was reported by the original study authors. We report the results of included studies using the descriptors “positive” for statistically significant associations with P values less than .05 (after multiple testing correction, if available) and “negative” for the lack of statistically significant (P ≥ .05) associations.

2.8 | Data synthesis

A descriptive synthesis was carried out using the extracted data and major findings of each included study. We have synthesised the data by listing the genetic associations of investigated variants with a specific outcome variable (LBD/DLB/PDD). If three or more studies investigated the genetic association between a single genetic variant and a specific outcome variable, we conducted either fixed or random-effects meta-analyses using the STATA 15.1 software (StataCorp LLC, TX, USA) and its “metan” command. Later, we grouped these genetic associations by their potential functional links to the complex aetiopathogenesis of LBD. We have discussed the potential functional implications of the reported genetic associations within the context of available literature.

3 | RESULTS

We identified and screened 5125 papers after removing the duplicates and found 75 papers eligible to be included in this systematic review. Figure 1 presents the study selection process in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) format. Our quality assessment using the Q-Genie rated 31 (41.3%) included studies as poor, 27 (36.0%) studies as moderate quality, and 17 (22.7%) studies as good (see Table S1). Statistically significant genetic associations have been reported between LBD and the genetic variants in A2M, APOE, BCHE, BCL7C, CHRFAM7A, CNTN1, ESRI, GABRB3, GBA, MAPT, NOS2, PSEN1, SCARB2, SNCA, TFAM, TREM2, UCHL1, and mitochondrial DNA (mtDNA) haplogroup H. Associations between DLB and variants in APOE, GBA, SNC, and MAPT and between PDD and variants in APOE and GBA have been replicated by two or more studies. There has been only one GWAS investigating DLB that has reported genome-wide significant associations between DLB and rs429358 (APOE), rs7681440 (SNCA), rs35749011 (GBA), rs897984 (BCL7/ STX1B), and rs1426210 (GBAB83) in its discovery stage. There has not been any GWAS investigating people with PDD so far.

3.1 | APOE

The APOE variants, especially its ε4 allele, are the most studied among all genetic variants in people with LBD. Apolipoprotein E (APOE) is involved in cholesterol mobilisation and redistribution during neuronal growth and injury, and it may promote β-amyloid aggregation. Among the 25 studies that investigated the association of APOE-ε4 with DLB, 21 have demonstrated a statistically significant association between APOE-ε4 and DLB (Table 1). The 21 positive studies included six good quality, eight moderate quality, and seven poor quality studies, and the negative studies included one good, one moderate, and two poor quality studies. We conducted a meta-analysis including data from 17 positive studies and all four negative studies (Figure 2). We did not include four positive studies, because they did not provide allele frequency data or used the same participants as another study. There was significant heterogeneity (χ² = 45.18, df = 21; P = .002) among the studies, and the random-effects meta-analysis confirmed that the APOE-ε4 is significantly associated with increased risk of DLB (pooled odds ratio [POR] = 2.70; 95% CI, 2.37-3.07; P < .001).
Moreover, statistically significant associations with probable reduced risk of DLB have been reported between APOE-ε2 and DLB.\textsuperscript{21-23,29} Similarly, one of the studies investigating the association between APOE-ε3 and DLB has reported statistically significant reduced risk for DLB.\textsuperscript{29} Furthermore, two moderate quality studies and one poor quality study including PD controls without dementia (PDND)\textsuperscript{32,42} have reported statistically significant associations between APOE-ε4 and PDD. Another moderate quality study has reported significantly increased frequency of APOE-ε4 in a LBD group including people with DLB and PDD compared to PDND controls.\textsuperscript{44} However, eight studies including two good, four moderate, and two poor quality studies did not find statistically significant association between APOE-ε4 and PDD.\textsuperscript{19,30,45-50} We conducted a meta-analysis including data from the four positive studies and eight negative studies (Figure 3). There was significant heterogeneity ($\chi^2 = 29.22, df = 11; P = .002$) among the studies, and the random-effects meta-analysis confirmed that the APOE-ε4 is significantly associated with increased risk of PDD (POR = 1.60; 95% CI, 1.21-2.11; $P = .001$).

3.2 | GBA

The glucosylceramidase beta gene (GBA) encoding the lysosomal glucosylceramidase (GBA) enzyme has been consistently associated with PD.\textsuperscript{51,52} GBA variants are likely to increase the risk of earlier onset cognitive impairment in PD. Six studies\textsuperscript{10,11,28,32,41,52} including four good quality studies have reported statistically significant associations between DLB and GBA variants including rs2230288,\textsuperscript{10} rs76763715,\textsuperscript{48} rs368060,\textsuperscript{32,52} rs35749011,\textsuperscript{11} and rs42101678 (Table 2). Moreover, two studies have reported statistically significant associations between GBA variants and PDD\textsuperscript{10,30} (Table 3).

3.3 | SNCA

α-synuclein encoding SNCA variants rs974711,\textsuperscript{19} rs1348224,\textsuperscript{19} and rs7681440\textsuperscript{11} have been associated with DLB. However, studies that investigated SNCA triplcation,\textsuperscript{53} SNCA variant rs104893877,\textsuperscript{54} and variants in α-synuclein interacting protein encoding SNCAIP\textsuperscript{55} did not find statistically significant associations with DLB. Moreover, SNCA variants rs10018362 and rs76899419 were significantly increased in PDD, and SNCA variants rs1372525, rs2583988, rs2619364, rs2619363, and rs2301135 were not significantly associated with PDD.\textsuperscript{56} Apart from the replicated association between DLB and rs7681440,\textsuperscript{11} the reported genetic association findings between LBD and other SNCA variants have not been replicated so far.

3.4 | MAPT

MAPT encodes tau protein. Two moderate\textsuperscript{57,58} and one poor quality\textsuperscript{59} studies have reported significant association between MAPT H1
haplotype and DLB, but two good quality studies have not replicated this finding. Moreover, a moderate quality study has reported associations between PDD and MAPT H1 haplotype and another probably protective variant rs1467967.60

### 3.5 Other genetic associations

Tables 2 and 3 present other reported genetic associations of DLB and PDD, respectively. The GWAS has replicated the association between DLB and rs7314908 of CNTN1.11 The reported genetic associations between DLB and rs897984 (BCL7C),11 2 bp in exon 6 of CHRFAM7A,17 rs1426210 (Gabrb3),11 mtDNA haplogroup H,25 SCARB2 variants24 need further replication. Conflicting evidence exists for the genetic associations of DLB with other variants in BCHE (K allele),33,61 NOS2,34,62 mtDNA,63 PSEN1,26,64 and TREM2.11,28,65 Studies that investigated the genetic associations of DLB with variants in A2M,66 AACT,29 ADORA1,67 BDNF,18 CYP2D6,68 DBH,77 LRRK2,69 NOS3,62 PARK7,70 PRGN,71 RAB39B,72 SNCB,73 TFAM,74 and TP75 did not find statistically significant associations. Moreover, two studies have reported conflicting evidence regarding the genetic associations between PDD and variants in ESR1.76,77 The reported genetic associations between PDD and variants in A2M,78 TFAM (rs2306604),74 and UCHL1 (rs4861387)79 have not been replicated so far. Studies that investigated the genetic associations of PDD with variants in BDNF,80 CYP2D6,81 IL-10,82 IL-18,82 MMP12,83 NAT2,84 PPARGC1A,85 PPARG,85 PSEN2,86 RAGE,87 SLC6A4,88 TOMM40,89 and TREM290 have reported negative findings.

### 4 DISCUSSION

This is the first systematic review of all genetic association studies that investigated people with LBD. We have summarised all reported genetic associations and have highlighted the genetic associations that have been replicated. The strengths of this systematic review include its broad inclusion criteria, searching multiple databases including grey literature, following PRISMA guidelines, and rigorous quality assessment using the Q-Genie instrument. However, we should acknowledge the limitations of excluding studies that were published in other languages, not including gene expression and epigenetic studies, and of substantial heterogeneity among the included studies. Apart from one exome sequencing study and one GWAS, other eligible studies were candidate gene association studies. Most
of them were small, and they have not reported sample size estimation or power analysis, so they were prone to type II error. They differed widely on their population characteristics, case definitions, selection of controls, and statistical analyses. Many studies did not employ appropriate statistical corrections for multiple testing, so their findings were prone to type I error. Most of the included studies have predominantly recruited Caucasian people, so their findings have limited generalisability. Furthermore, the second GWAS investigating DLB was published after the completion of this systematic review in May 2019. The GWAS confirmed the genetic associations of DLB with APOE-ε4 and GBA, and it reported a suggestive association between DLB and ZFPM1. Moreover, the first genome-wide analysis of copy number variants (CNVs) in people with DLB was also published in May 2019. Five CNV regions including ADGRG7, TFG, PDZD2, LAPTM4B, MSR1, NME1, NME2, and SPAG9 were reported to have genome-wide significant associations with DLB.
APOE-ε4 variant has the largest body of evidence in this topic.\textsuperscript{16-41} Two GWAS have confirmed the genome-wide significant association between APOE-ε4 and DLB. Our meta-analyses have confirmed this association, and the genetic association between APOE-ε4 and PDD. Similar to this genetic association, the molecular genetics of LBD has been hypothesised to overlap with known genetic associations of AD and PD.\textsuperscript{8} However, the genetic overlap is limited to only a few genes including APOE, ESR1, MAPT, PSEN1, TFAM, and TREM2 that have been reported to be associated with both LBD and AD.\textsuperscript{92-94} Despite the overlap in genetics of LBD, AD, and PD, there are substantial variations in their clinical presentation and longitudinal progression. These variations may be explained by genetic risk variants specific to LBD, gene environment interactions, epigenetics, and various environmental factors. There is a need for more robust studies investigating gene environment interactions in people with LBD. A recent genome-wide meta-analysis has identified 29 risk loci for AD,\textsuperscript{93} and only two of those genes, APOE and TREM2, have been reported to be associated with LBD so far. Notwithstanding the limited power of most of the LBD genetic association studies, several genes that have not been associated with AD such as CNTN1, BCL7C, and GABRB3, and several genes that have been associated with PD such as GBA, SNCA, UCHL1, and SCARB2 have been associated with LBD. These genetic associations imply that the molecular pathology underlying the two most prevalent neurodegenerative dementias may have substantial differences. Further studies are warranted for replicating these genetic associations, and for investigating their functional implications, and biomarker potential. Future LBD genetic association studies should not limit their focus only on known AD or PD risk genes, and there is a need for larger GWAS and transcriptomic studies investigating the molecular genetics of LBD.

LBD is an α-synucleinopathy,\textsuperscript{95} and its reported genetic associations indicate the importance of autophagy lysosomal pathway (ALP), ubiquitin proteasome system (UPS), oxidative stress, and mitochondrial dysfunction in its complex etiopathology. Aggregation of α-synuclein leads to the formation of Lewy bodies,\textsuperscript{96} and the genes that are implicated in increased α-synuclein aggregation either directly (SNCA and PSEN1\textsuperscript{97}) or indirectly (MAPT\textsuperscript{57-60}) have been associated with LBD.\textsuperscript{98} SNCA variants and MAPT H1 subhaplotypes have been

### TABLE 2  The studies that have reported other statistically significant genetic associations of dementia with Lewy bodies

| Study                     | Gene   | Cases:Controls | Variant(s)                       | OR (95% CI) | P value |
|---------------------------|--------|----------------|----------------------------------|-------------|---------|
| Vijayaraghavan et al\textsuperscript{23} | BCHE   | 174:86         | One or two K alleles             | 0.49 (0.34-0.71)\textsuperscript{a} | P < .001 |
| Guerreiro et al\textsuperscript{11}  | BCL7C  | 1743:4454      | rs897984                         | 0.74 (0.67-0.82) | P = 3.30×10\textsuperscript{-9} |
| Feher et al\textsuperscript{17}    | CHRFAM7A | 35:175       | 2 bp deletion at 497-498 in exon 6 | 3.76 (2.21-6.39)\textsuperscript{a} | P = .001 |
| Guerreiro et al\textsuperscript{11}  | CNTN1  | 1743:4454      | rs7314908                        | 1.51 (1.27-1.79) | P = 2.32×10\textsuperscript{-6} |
| Guerreiro et al\textsuperscript{11}  | GABRB3 | 1743:4454      | rs1426210                        | 1.34 (1.21-1.48) | P = 2.62×10\textsuperscript{-8} |
| Nalls et al\textsuperscript{10}    | GBA    | 721:1962       | “Mutations”                       | 8.28 (4.78-14.88) | P = 5.52×10\textsuperscript{-15} |
| Nalls et al\textsuperscript{10}    | GBA    | 721:1962       | rs2230288                        | 2.72 (1.38-5.54) | P = .006 |
| Keogh et al\textsuperscript{41}    | GBA    | 87:93          | 5 GBA variants                    | NR          | P = .043 |
| Mata et al\textsuperscript{52}     | GBA    | 57:554         | rs76763715 or rs368060            | 10.00 (1.7-139.8) | P = .045 |
| Tsuang et al\textsuperscript{52}   | GBA    | 79:391         | “Pathogenic GBA mutation carriers” | 7.60 (1.8-31.9) | P = .001 |
| Keogh et al\textsuperscript{28}    | GBA    | 58:368         | rs421016                         | NR          | P = .008 |
| Guerreiro et al\textsuperscript{11}  | GBA   | 1743:4454      | rs35749011                       | 2.55 (1.88-3.46) | P = 1.78×10\textsuperscript{-9} |
| Labbe et al\textsuperscript{57}    | MAPT   | 431:1049       | H1G haplotypes                   | 3.30 (1.34-8.12) | P = .002 |
| Labbe et al\textsuperscript{57}    | MAPT   | 431:1049       | H1L haplotypes                   | 0.37 (0.15-0.92) | P = .041 |
| Labbe et al\textsuperscript{58}    | MAPT   | 442:1679       | rs143624519                      | 5.76 (1.62-20.51) | P = .007 |
| Cervera-Carles et al\textsuperscript{59} | MAPT | 51:325         | H1 allele                        | 1.81 (1.05-3.14) | P = .032 |
| Chinnery et al\textsuperscript{25} | mtDNA  | 84:179         | Haplogroup H                     | NR          | P = .034 |
| Xu et al\textsuperscript{24}       | NOS2   | 22:101         | (CCTTT)n repeat                  | 5.04 (1.5-16.9) | P < .01 |
| Geiger et al\textsuperscript{16}   | PSEN1  | 111:222        | rs17125721                       | 2.10 (1.04-3.76) | P = .035 |
| Guella et al\textsuperscript{19}   | SNCA   | 922:971        | rs974711                         | 1.22 (1.07-1.38) | P < .002 |
| Guella et al\textsuperscript{19}   | SNCA   | 922:971        | rs1348224                        | 0.74 (0.65-0.85) | P < .002 |
| Bras et al\textsuperscript{24}     | SNCA   | 788:2624       | Not specified                    | NR          | P = 3.7×10\textsuperscript{-5} |
| Guerreiro et al\textsuperscript{11}  | SNCA  | 1743:4454      | rs7691440                        | 0.73 (0.66-0.81) | P = 6.39×10\textsuperscript{-10} |
| Bras et al\textsuperscript{24}     | SCARB2 | 788:2624       | Not specified                    | NR          | P < .001 |
| Keogh et al\textsuperscript{28}    | TREM2  | 58:368         | p.R62H                            | 3.20 (1.7-27) | P = .002 |

Abbreviations: mtDNA, mitochondrial DNA; NR, not reported; OR, odds ratio.

\textsuperscript{a}Higher K allele frequency in controls vs DLB case group.

\textsuperscript{b}Odds ratios (ORs) were calculated using the reported allele frequency data.
### TABLE 3  The studies that have reported statistically significant genetic associations of Parkinson’s disease dementia

| Study | Gene | Cases/Controls | Variant(s) | OR (95% CI) | P value |
|-------|------|----------------|------------|-------------|---------|
| Sleeers et al78 | A2M | 9 (LBD):283 | D-allele | 0.67 (0.23-1.96) | P = .009 |
| Harhangi et al42 | APOE | 26:4805 | ε2, ε3, ε4 | 2.20 (1.7-2.9) | Significant |
| Tsuang et al92 | APOE | 81:269 | ε2, ε3, ε4 | 3.10 (1.7-5.6) | P = 1.94 × 10-5 (ε4 allele) |
| Arai et al53 | APOE | 14:49 (PDND) | ε2, ε3, ε4 | 4.68 (1.64-13.36) | P < .001 |
| Lindqvist et al94 | APOE | 55 (PD) + 101 (DLB):92 (PDND) | ε4 | 2.26 (1.18-4.34) | P < .014 |
| Isoe-Wada et al76 | ESR1 | 13:51 | Pnull | 2.81 (1.16-6.83) | P < .02 (PDD vs CTL) |
| | 13:71 (PDND) | | | 3.34 (1.41-7.93) | P = .0073 (PDD vs PDND) |
| Nalls et al10 | GBA | 151:1962 | “Mutations” | 6.48 (2.53-15.37) | P = 9.66 × 10-6 |
| Nalls et al10 | GBA | 151:1962 | rs2230288 | 3.91 (1.41-10.86) | P = .009 |
| Meeus et al8 | GBA | 75 (PDD) + 99 (DLB): 626 | “Mutant alleles” | 3.01 (1.25-7.20) | P = .010 (LBD vs CTL) |
| Seto-Salvia et al60 | MAPT | 41(LBD):374 | H1 haplotype | 2.69 (1.47-4.95) | P = .001 |
| Seto-Salvia et al60 | MAPT | 41(LBD):374 | rs1467967 | 0.54 (0.34-0.85) | P = .007b |
| Guella et al19 | SNCA | 198:971 | rs10018362 | 1.77 (1.28-2.45) | P = .002 |
| Guella et al19 | SNCA | 198:971 | rs7689942 | 2.10 (1.39-3.17) | P = .002 |
| Gatt et al74 | TFAM | 63:1410 | rs2306604 | 2.09 (1.13-3.89) | P = .024 (AA genotype vs AG and GG) |
| Shiba et al79 | UCHL1 | 39:137 | rs4861387 | 1.20 (0.58-2.50) | P = .03 |

Abbreviations: CTL, controls (CTL); DLB, dementia with Lewy bodies; LBD, Lewy body dementia; OR, odds ratio; PDD, Parkinson’s disease dementia; PDND, Parkinson disease patients without dementia.

*P value has not been reported.

bDecreased frequency in LBD.

cOdds ratios (OR) were calculated using the reported allele frequency data.

Potential interactions between these variants may lead to synergistic neurodegenerative effects of amyloid, tau, and α-synuclein deposition.59,60,99,100 Moreover, PSEN1 variants may contribute to neurodegeneration in LBD through increased amyloid deposition.97 The L435F PSEN1 minor allele reportedly leads to progressive loss of cortical neurons, increased apoptosis, astrogliosis, and microgliosis in PSEN1 knock-in mice.102

The genetic associations between GBA variants and PD are well known, and the people with PD carrying GBA variants are at higher risk for developing PDD.103,104 However, little is known about how GBA variants contribute to neurodegeneration in people with LBD. ALP and UPS are important cellular systems responsible for the degradation of misfolded proteins.105 GBA variants are likely to impair ALP and to cause cytoplasmic accumulation of misfolded proteins. Lysosomal dysfunction coupled with higher misfolded protein burden may overwhelm the UPS and autophagy pathways and may increase α-synuclein aggregation.51 Functional loss of GBA and consequent impaired lysosomal protein degradation have been reported to cause α-synuclein aggregation and neurotoxicity in stem cell-derived neurons.106 Such aggregated α-synuclein may set off a self-propagating disease by inhibiting neuronal lysosomal activity.106 Moreover, SCARB2 gene encodes a lysosomal membrane protein that transports GBA to lysosomes, and its deficiency may lead to reduced GBA activity and α-synuclein accumulation.107 Furthermore, UCHL1 is essential for reuse of free ubiquitin and hydrolysis of substrates by neuronal UPS, and its loss of function may contribute to the formation of Lewy bodies.79,108

The mitochondrial cascade hypothesis for AD states that an individual’s mtDNA determines baseline mitochondrial function that declines with age and environmental insults resulting in AD pathology.109 As LBD has been found to be associated with mtDNA haplogroup H, independent of APOE genotype,25 the similar mitochondrial cascade hypothesis can be considered for LBD. APP has been found to be targeted to the mitochondria, and its progressive accumulation on mitochondrial membrane may cause mitochondrial dysfunction.110 TFAM encodes mitochondrial transcription factor A (TFAM) that is essential for mitochondrial transcription and mtDNA replication. TFAM variants impairing its function may lead to mitochondrial dysfunction and neurodegeneration.111 TFAM over-expression has been reported to improve hippocampal long-term potentiation and motor learning memory in mice.106 It has been found to reduce expression of inflammatory mediators such as interleukin-1β and to reduce mtDNA damage in microglia.111 Moreover, mitochondrial dysfunction in LBD may lead to a vicious cycle by producing more reactive oxygen species that in turn causing more mitochondrial oxidative damage.112 Resulting oxidative stress may lead to α-synuclein aggregation worsening the vicious cycle by impairing more mitochondria.112 Further studies are warranted for investigating these hypotheses and the molecular mechanisms underlying mitochondrial dysfunction in LBD.

A2M, TREM2, CNTN1, NOS2, and ESR1 are implicated in protein degradation and/or neuronal survival. A2M encodes an antiprotease that inhibits various proteinases, and it may contribute to the formation of Lewy bodies and amyloid plaques.113,114 TREM2 variants have
been associated with early-onset dementia,\textsuperscript{115} and they may impair autophagy and clearance of misfolded proteins.\textsuperscript{116} CNTN1 encodes contactin 1 that modulates remyelination and neuroinflammation and regulates the activity of APP cleaving enzyme BACE1.\textsuperscript{11,117} NOS2 generates nitric oxide in neurons and microglia, and it promotes cell survival though inhibition of apoptosis.\textsuperscript{118} Less NOS2 CCTT repeats lead to reduced level of nitric acid synthase that may increase oxidative stress and may impair neuronal survival in LBD.\textsuperscript{38} BCHE encodes acetylcholinesterase that regulates the activity of APP cleaving enzyme BACE1. It has been reported that estradiol-17-\textbeta and ESR1 activation may upregulate APOE-\textepsilon4 expression,\textsuperscript{122} and there is a need for further studies investigating the functional implications of reported genetic associations between ESR1 variants and LBD. Moreover, cholinergic system dysfunction may play an important role in LBD pathology. The CHRFAM7A variant results in nearly 30\% less butyrylcholinesterase activity,\textsuperscript{33} and it has been associated with reduced tau phosphorylation in people with dementia.\textsuperscript{120} The CHRFAM7A variant has been found to be significantly less common among people with DLB.\textsuperscript{33} Additionally, the reported genetic association between CHRFAM7A and LBD may highlight the importance of cholinergic system dysfunction in LBD.\textsuperscript{17,124}

CHRFAM7A is a duplicated gene complex including CHRNA7 that encodes neuronal acetylcholine receptor subunit \textalpha-7 (nAChRa7). nAChRa7 has been implicated in the pathology of several neuropsychiatric disorders, and it is involved in memory, sensory information processing, and neuronal survival.\textsuperscript{125}

In comparison with the field of molecular genetics of AD or PD, pertinent research investigating genetics of LBD is still at an early stage. The field of LBD genetics has recently joined the GWAS era.\textsuperscript{11,90} None of the reported genetic associations warrant routine genetic testing in clinical settings at present, and the field is far from translating the knowledge of genetics to clinical diagnostic and therapeutic applications. As a definite diagnosis of DLB can be confirmed only by post-mortem neuropathological verification,\textsuperscript{1} it is difficult to rule out misclassification bias in any candidate gene association study or GWAS investigating people living with LBD. However, there is a need for larger GWAS and broader international collaborations for identifying more LBD associated genes. The reliability of clinical diagnoses of LBD should be pathologically verified by post-mortem examination of brains of a few study participants. Then, the field can catch up with the post-GWAS era\textsuperscript{126} in understanding the molecular mechanisms underlying the identified genetic associations. Meanwhile, there is a need for more hypothesis-driven studies for replicating reported genetic associations of LBD and for exploring their functional implications. Gene expression studies and transcriptomic analyses of post-mortem LBD brains or of circulating exosomes of people living with LBD may help understanding the functional significance of the genetic associations and their molecular networks.\textsuperscript{127-130} Future hypothesis-driven studies should prioritise the identified genetic associations of LBD that do not overlap with known AD risk genes. Such studies may advance our understanding of molecular mechanisms underlying neurodegeneration in LBD and may aid the discovery of novel biomarkers and therapeutic targets for LBD.

**CONFLICT OF INTEREST**

None declared.

**AUTHOR CONTRIBUTIONS**

HS and APR conceived the study, and HS wrote the initial study protocol. The systematic review team included HS, RS, and HM. They completed necessary quality assessment and data extraction. APR completed all data analyses. HS wrote the initial manuscript with the supervision of APR. All authors were involved in further critical revisions of the manuscript, and all authors have approved the final version of the manuscript.

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

**ORCID**

Anto P. Rajkumar https://orcid.org/0000-0003-3203-6326

**REFERENCES**

1. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: fourth consensus report of the DLB consortium. Neurology. 2017;89(1):88-100.
2. Walker Z, Possin KL, Boeve BF, Aarsland D. Lewy body dementias. Lancet. 2015;386(10044):1683-1697.
3. Oesterhus R, Soennesyn H, Rongve A, Ballard C, Aarsland D, Vossius C. Long-term mortality in a cohort of home-dwelling elderly with mild Alzheimer’s disease and Lewy body dementia. Dement Geriatr Cogn Disord. 2014;38(3-4):161-169.
4. Vossius C, Rongve A, Testad I, Wimo A, Aarsland D. The use and costs of formal care in newly diagnosed dementia: a three-year prospective follow-up study. Am J Geriatr Psychiatry. 2014;22(4):381-388.
5. Mueller C, Ballard C, Corbett A, Aarsland D. The prognosis of dementia with Lewy bodies. 162017:390-398.
6. Tsuang DW, Di Giacomo L, Bird TD. Familial occurrence of dementia with Lewy bodies. Am J Geriatr Psychiatry. 2004;12(2):179-188.
7. Nervi A, Reitz C, Tang MX, et al. Familial aggregation of dementia with Lewy bodies. Arch Neurol. 2011;68(1):90-93.
8. Meeus B, Verstraeten A, Crousiers D, et al. DLB and PDD: a role for mutations in dementia and Parkinson disease genes? Neurobiol Aging. 2012;33(3):629 e625-629 e618.
9. Romo-Gutiérrez D, Yescas P, Lopez-Lopez M, Boll MC. Genetic factors associated with dementia in Parkinson’s disease (PD). Gac Med Mex. 2015;151(1):110-118.
10. Nalls MA, Duran R, Lopez G, et al. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013;70(6):727-735.
11. Guerreiro R, Ross OA, Kun-Rodrigues C, et al. Investigating the genetic architecture of dementia with Lewy bodies: a two-stage genome-wide association study. Lancet Neurol. 2018;17(1):64-74.
12. Guerreiro R, Escott-Price V, Hernandez DG, et al. Heritability and genetic variance of dementia with Lewy bodies. Neurobiol Dis. 2019;127:492-501.
13. Sohani ZN, Meyre D, de Souza RJ, et al. Assessing the quality of published genetic association studies in meta-analyses: the quality of genetic studies (Q-Genie) tool. BMC Genet. 2015;16:50.
14. Sohani ZN, Sarma S, Alyass A, et al. Empirical evaluation of the Q-genie tool: a protocol for assessment of effectiveness. BMJ Open. 2016;6(6):e010403.

15. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336-341.

16. Harrington CR, Louwagie J, Rossau R, et al. Influence of apolipoprotein E genotype on senile dementia of the Alzheimer and Lewy body types. Significance for etiological theories of Alzheimer's disease. Am J Pathol. 1994;145(6):1472-1484.

17. Feher A, Juhasz A, Rimanczcy l, Csibi E, Kalman J, Janka Z. Association between a genetic variant of the alpha-7 nicotinic acetylcholine receptor subunit and four types of dementia. Dement Geriatr Cogn Disord. 2009;28(1):56-62.

18. Feher A, Anna J, Rimanczcy l, Janos K, Janka Z. Association between BDNF Val66Met polymorphism and Alzheimer disease, dementia with Lewy bodies, and park disease. Alzheimer Disease & Associated Disorders. 2009;23(3):224-228.

19. Geulla I, Evans DM, Szu-Tu C, et al. Alpha-synuclein genetic variability: a biomarker for dementia in Parkinson disease. Ann Neurol. 2016;79(6):991-999.

20. Akatsu H, Kamino K, Yamagata H, et al. Increased incidence of dementia with Lewy bodies in patients carrying the ε4 allele of apo-lipoprotein E. Psychogeriatrics. 2004;4(2):24-32.

21. Benjamin R, Leake A, Ince PG, et al. Effects of apolipoprotein E genotype on cortical neuropathology in senile dementia of the Lewy body and Alzheimer's disease. Neurodegeneration. 1999;4(4):443-448.

22. Borge G, Sando SB, Rongve A, Aarsland D, White LR. Apolipoprotein E ε2 genotype delays onset of dementia with Lewy bodies in a Norwegian cohort. J Neurol Neurosurg Psychiatry. 2014;85(11):1227-1231.

23. Borroni B, Grassi M, Costanzi C, Archetti S, Caimi L, Padovan 1. APOE genotype and cholesterol levels in lewy body dementia and Alzheimer disease: investigating genotype-phenotype effect on disease risk. Am J Geriatr Psychiatry. 2006;14(12):1022-1031.

24. Bras J, Guerreiro R, Darwent L, et al. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet. 2014;23(23):6139-6146.

25. Chimney PF, Taylor GA, Howell N, et al. Mitochondrial DNA haplogroups and susceptibility to AD and dementia with Lewy bodies. Neurology. 2000;55(2):302-304.

26. Geiger JT, Ding J, Crain B, et al. Next-generation sequencing reveals substantial genetic contribution to dementia with Lewy bodies. Neurol Dis. 2016;94:55-62.

27. Huckvale C, Richardson AM, Mann DM, Pickering-Brown SM. Debrisoquine hydroxylase gene polymorphism (CYP2D6*4) in dementia with Lewy bodies. J Neurol Neurosurg Psychiatry. 2003;74(1):135-136.

28. Kegoh MJ, Wei W, Wilson I, et al. Genetic compendium of 1511 human brains available through the UK Medical research council brain banks network resource. Genome Res. 2017;27(1):165-173.

29. Lamb H, Christie J, Singleton AB, et al. Apolipoprotein E and alpha-1 antichymotrypsin polymorphism genotyping in Alzheimer's disease and in dementia with Lewy bodies. Distinctions between diseases. Neurology. 1998;50(2):388-391.

30. Meeus B, Verstraeten A, Nuytemans K, et al. Dementia with Lewy bodies: a role for dementia and Parkinson's disease genes? Mov Disord. 2010;25:S614.

31. Singleton AB, Wharton A, O'Brien KK, et al. Clinical and neuropathological correlates of apolipoprotein E genotype in dementia with Lewy bodies. Dement Geriatr Cogn Disord. 2002;14(4):167-175.
52. Mata IF, Samii A, Schnee SH, et al. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. *Arch Neural*. 2008;65(3):379-382.

53. Johnson J, Hague SM, Hansom M, et al. SNCA multiplication is not a common cause of Parkinson disease or dementia with Lewy bodies. *Neurology*. 2004;63(3):554-556.

54. Higuchi S, Arai H, Matsushita S, et al. Mutation in the alpha-synuclein gene and sporadic Parkinson's disease. *Alzheimer's disease, and dementia with Lewy bodies. Exp Neurol*. 1998;153(1):164-166.

55. Busby J, O'Brien KK, Gibson AM, et al. Dementia with Lewy bodies: no association of polymorphisms in the human synphilin gene. *Neurogenetics*. 2004;5(4):251-252.

56. De Marco EV, Tarantino P, Rocca FE, et al. Alpha-synuclein promoter haplotypes and dementia in Parkinson's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147(3):403-407.

57. Labbe C, Ogaki K, Lorenzo-Betancor O, et al. Role for the microtubule-associated protein tau variant p.A152T in risk of alpha-synucleinopathies. *Neurology*. 2015;85(19):1680-1686.

58. Labbe C, Heckman MG, Lorenzo-Betancor O, et al. MAPT haplotype H1G is associated with increased risk of dementia with Lewy bodies. *Alzheimer's Dement*. 2016;12(12):1297-1304.

59. Cervera-Carles L, Pagonabarraga J, Pascual-Sedano B, et al. Copy number variation analysis of the 17q21.31 region and its role in neurodegenerative diseases. *Am J Med Genet B Neuropsychiatr Genet*. 2016;171B(2):175-180.

60. Seto-Salvia N, Clarimon J, Pagonabarraga J, et al. Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. *Arch Neurol*. 2011;68(3):359-364.

61. Singleton AB, Gibson AM, Edwards SJ, McKeith IG, Morris CM. Butyrylcholinesterase K: an association with dementia with Lewy bodies. *Lancet*. 1998;351(9118):1818.

62. Singleton AB, Gibson AM, McKeith IG, Ballard CG, Edwards SJ, Morris CM. Nitric oxide synthase gene polymorphisms in Alzheimer's disease and dementia with Lewy bodies. *Neurosci Lett*. 2001;303(1):33-36.

63. Gu G, Reyes PE, Golden GT, et al. Mitochondrial DNA deletions/rearrangements in Parkinson disease and related neurodegenerative disorders. *J Neuropathol Exp Neurol*. 2002;61(7):634-639.

64. Singleton AB, Lamb H, Leake A, et al. No association between a polymorphism in the presenilin 1 gene and dementia with Lewy bodies. *Neuropathol Appl Neurobiol*. 1997;23(8):637-639.

65. Walton RL, Soto-Oortolaza AI, Murray ME, et al. TREM2 p. R47H substitution is not associated with dementia with Lewy bodies. *Neurology, Genetics*. 2016;2(4):e85.

66. Singleton AB, Gibson AM, McKeith IG, et al. α2-macroglobulin polymorphisms in Alzheimer's disease and dementia with Lewy bodies. *Neuropathol Appl Neurobiol*. 1999;17(10):1507-1510.

67. Blauwendraat C, Nalls MA, Federoff M, et al. ADORA1 mutations are not a common cause of Parkinson's disease and dementia with Lewy bodies. *Mov Disord*. 2017;32(2):298-299.

68. Furuno T, Kawanishi C, Ikese I, et al. No evidence of an association between CYP2D6 polymorphisms among Japanese and dementia with Lewy bodies. *Psychiatry Clin Neurosci*. 2001;55(2):89-92.

69. Heckman MG, Soto-Oortolaza AI, Contreras MY, et al. LRRK2 variation and dementia with Lewy bodies. *Parkinsonism Relat Disord*. 2016;31:98-103.

70. Morris CM, O'Brien KK, Gibson AM, Hardy JA, Singleton AB. Polymorphism in the human DJ-1 gene is not associated with sporadic dementia with Lewy bodies or Parkinson's disease. *Neurosci Lett*. 2003;352(2):151-153.

71. Benussi L, Ghidoni R, Pegoiani E, Moretti DV, Zanetti O, Binetti G. Progranulin Leu271LeufsX10 is one of the most common FTLD and CBS associated mutations worldwide. *Neurobiol Dis*. 2009;33(3):379-385.

72. Hodges K, Brewer SS, Labbe C, et al. RAB39B gene mutations are not a common cause of Parkinson's disease or dementia with Lewy bodies. *Neurobiol Aging*. 2016;45:107-108.

73. Ohtake H, Limprasert P, Fan Y, et al. Beta-synuclein gene alterations in dementia with Lewy bodies. *Neurology*. 2004;63(5):805-811.

74. Gatt AP, Jones EL, Francis PT, Ballard C, Bateman JM. Association of a polymorphism in mitochondrial transcription factor A (TFAM) with Parkinson's disease dementia but not dementia with Lewy bodies. *Neurosci Lett*. 2013;557:177-180.

75. Hussain RI, Ballard CG, Edwards SJ, Morris CM. Transferrin gene polymorphism in Alzheimer's disease and dementia with Lewy bodies in humans. *Neurosci Lett*. 2002;317(1):13-16.

76. Isoe-Wada K, Maeda M, Yong J, et al. Positive association between an estrogen receptor gene polymorphism and Parkinson's disease with dementia. *Eur J Neurol*. 1999;6(4):431-435.

77. Mattila KM, Rinne JO, Rytta M, Laippala P, Lehtimaki T. Lack of association between an estrogen receptor 1 gene polymorphism and Parkinson's disease with dementia. *Acta Neurol Scand*. 2002;106(3):128-130.

78. Sleegers K, Roks G, Theuns J, Aulchenko YS, Rademakers R, Cruts M, van Gool WA, van Broeckhoven C, Heutink P, Oostra BA, van Swieten JC, van Duijn CM. Familial clustering and genetic risk for dementia in a genetically isolated Dutch population. *Brain*. 2004;127(Pt 7):1641-1649.

79. Shibata N, Motoy I, Tomiyama H, et al. Lack of genetic association of the UCHL1 gene with Alzheimer's disease and Parkinson's disease with dementia. *Dement Geriatr Cogn Disord*. 2012;33(4):250-254.

80. Białecka M, Kurzawski M, Roszmann A, et al. BDNF G196A (Val66Met) polymorphism associated with cognitive impairment in Parkinson's disease. *Neurosci Lett*. 2014;561:86-90.

81. Golab-Janowska M, Honczarenko K, Gawronska-Szlakar B, Potemkowski A. CYP2D6 gene polymorphism as a probable risk factor for Alzheimer's disease and Parkinson's disease with dementia. *Neural Neurochir Pol*. 2007;41(2):113-121.

82. Liu Z, Guo J, Wang Y, et al. Lack of association between IL-10 and IL-18 gene promoter polymorphisms and Parkinson's disease with cognitive impairment in a Chinese population. *Sci Rep*. 2016;6:21901.

83. Białecka M, Kurzawski M, Vlakova T, et al. Effects of common functional MMP12 gene polymorphisms on PD in a Polish population. *Neural Neurochir Pol*. 2017;51(5):347-353.

84. Golab-Janowska M, Honczarenko K, Gawronska-Szlakar B, Potemkowski A. The role of NAT2 gene polymorphism in aetiology of the most frequent neurodegenerative diseases with dementia. *Neural Neurochir Pol*. 2007;41(5):388-394.

85. Shibata N, Motoy I, Tomiyama H, et al. Lack of genetic associations of PPAR-gamma and PGC-1alpha with Alzheimer's disease and Parkinson's disease with dementia. *Dement Geriatr Cogn Dis Extra*. 2013;3(1):161-167.

86. Suzuki A, Shibata N, Kasanuki K, et al. Genetic association between presenilin 2 polymorphisms and Alzheimer's disease and dementia of Lewy body type in a Japanese population. *Dementia and Geriatric Cognitive Disorders Extra*. 2016;6(1):90-97.

87. Takeshita Y, Shibata N, Kasanuki K, et al. Genetic association between RAGE polymorphisms and Alzheimer's disease and Lewy body dementias in a Japanese cohort: a case–control study. *Int J Geriatr Psychiatry*. 2017;32(12):1241-1246.

88. Creese B, Ballard C, Aarsland D, Londos E, Sharp S, Jones E. Determining the association of the 5HTTLPR polymorphism with delusions and hallucinations in Lewy body dementias. *Am J Geriatr Psychiatry*. 2014;22(6):580-586.
89. Mengel D, Thelen M, Balzer-Geldsetzer M, et al. TREM2 rare variant p.R47H does not associated with Parkinson's disease. *Parkinsonism Relat Disord*. 2016;23:109-111.

90. Rongve A, Witoelar A, Ruiz A, et al. GBA and APOE ε4 associate with sporadic dementia with Lewy bodies in European genome wide association study. *Sci Rep*. 2019;9(1):7013.

91. Kun-Rodrigues C, Orme T, Carmona S, et al. A comprehensive screening of copy number variability in dementia with Lewy bodies. *Neurobiol Aging*. 2019;75:223 e221-223 e210.

92. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database. *Nat Genet*. 2007;39(1):17-23.

93. Jansen IE, Savage JE, Watanabe K, et al. Mitochondria and Alzheimer's disease: the mitochondrial dysfunction axis. *Hum Mol Genet*. 2019;28(4):357-360.

94. Xia D, Watanabe H, Wu B, et al. Presenilin-1 knockin mice reveal the role of Gpi-anchored axonal glycoproteins in neural development and neurological disorders. *Mol Cell Neurosci*. 2017;81:49-63.

95. Colton CA, Wilcock DM, Wink DA, Davis J, Van Nostrand WE, Vitek MP. The effects of NOS2 gene deletion on mice expressing mutated human ApoE. *J Alzheimers Dis*. 2008;15(4):571-587.

96. Ji Y, Usakani K, Wada-Isoe K, Adachi Y, Nakashima K. Estrogen receptor gene polymorphisms in patients with Alzheimer's disease, vascular dementia and alcohol-associated dementia. *Dement Geriatr Cogn Disord*. 2000;11(3):119-122.

97. Amtul Z, Wang L, Westaway D, Rizmahel RF. Neuroprotective mechanism conferred by 17beta-estradiol on the biochamical basis of Alzheimer's disease. *Neuroscience*. 2010;169(2):781-786.

98. Fernandez-Martinez M, Ecoloroaristizabal Martin X, Blanco Martin E, et al. Oestrogen receptor polymorphisms are an associated risk factor for mild cognitive impairment and Alzheimer disease in women APOE (varepsilon4) carriers: a case-control study. *BMJ Open*. 2013;3(9):e003200.

99. Rajkumar AP, Bidkhori G, Shoaie S, et al. Postmortem cortical transcriptionomics of Lewy body dementia reveal mitochondrial dysfunction.
and lack of neuroinflammation. Am J Geriatr Psychiatry. 2020;28:75-86.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.