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

Short running title: Genetics of Lewy body dementia

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Abstract

Objectives: Lewy body dementia (LBD) causes more morbidity, disability and earlier mortality than Alzheimer's 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: 8521 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 *APOE*-ε4 is significantly associated with dementia with Lewy bodies (pooled odds ratio (POR)= 2.70; 95%CI 2.37-3.07; p<0.001) and Parkinson's disease dementia (POR=1.60; 95%CI 1.21-2.11; p=0.001). Other reported genetic associations that need further replication include variants in *A2M, BCHE-K, BCL7C, CHRFAM7A, CNTN1, ESR1, GABRB3, MAPT*, 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 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

- Lewy Body Dementia
- Genetics
- Parkinson disease
- Apolipoproteins E
- Genetic association studies

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

Introduction

Lewy body dementia (LBD) is the second most common neurodegenerative dementia after the dementia in Alzheimer's disease (AD), and it accounts for 15-30% of all neurodegenerative dementias[1,2]. LBD comprises 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[5]. The search for disease modifying drugs and reliable peripheral biomarkers for LBD is still ongoing[2].

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[6,7]. Siblings of probands with DLB have been reported to have significantly higher risk of developing DLB than the siblings of probands with AD[7]. Research in these families has supported a role for genes implicated in both AD (*APP*, *PSEN1*, *PSEN2*, *PGRN*, *PRNP*) and Parkinson's disease (PD) (*SNCA, SNCB, LRRK2, GBA*) with the development of DLB and PDD[8]. 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*[9]. While the variants in *APOE* and *GBA* have been associated with both DLB and PDD, the associations are stronger for DLB over PDD[10]. 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[11]. It estimated 36% heritability of DLB, and it confirmed the

associations between DLB and variants in *APOE*, *SNCA*, and *GBA*[11]. 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[12].

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.

Methods

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).

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 3rd February 2018 and to English. Reference lists of the studies included in the review were explored for identifying other potentially eligible studies.

Eligibility criteria: We included all genetic association studies that satisfied the following inclusion criteria, i) they were human studies. Studies on animals or cell lines were not included, ii) they presented original research data, iii) participants in at least one study group were clinically diagnosed to have DLB or PDD or LBD, iv) 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.

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.

Data extraction: We extracted the following data, i) population characteristics including their mean age and ethnicity, (ii) sample size in each study group, iii) definition of the phenotype, iv) investigated genetic variant(s), v) genotyping method, vi) study findings with effect size and p-values, vii) statistical correction for multiple testing, viii) statistical analyses addressing the effects of potential confounders.

Quality assessment: We assessed the quality of eligible studies using the Quality of genetic association studies tool (Q-Genie)[13]. The Q-Genie assesses the following 11 dimensions, (i)

the rationale for study, (ii) selection and definition of outcome, (iii) selection and comparability of comparison groups, (iv) technical classification of the genetic variant(s), (v) non-technical classification of the genetic variant(s), (vi) other sources of bias, (vii) sample size and power, (viii) a priori planning of statistical analyses, (ix) statistical methods and control for confounding, (x) tests of assumptions and inferences for the genetic analyses, and (xi) appropriate interpretation of the study results. Each dimension is scored on a scale from one (poor) to seven (excellent). For studies with control group, Q-Genie total scores ≤35 indicate poor quality, total scores more than 45 indicate good quality, and total scores between 36 and 45 indicate moderate quality. The reliability and validity of the Q-Genie tool has already been demonstrated[14]. 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).

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 0.05 (after multiple testing correction, if available), and 'negative' for the lack of statistically significant (p≥0.05) associations.

Data synthesis: A descriptive synthesis was carried out using the extracted data and major findings of each included study. We have synthesized 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.

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 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) format[15]. 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 supplementary table-1). Statistically significant genetic associations have been reported between LBD and the genetic variants in *A2M*, *APOE*, *BCHE*, *BCL7C*, *CHRFAM7A*, *CNTN1*, *ESR1*, *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 (*BCL7C/ STX1B*), and rs1426210 (*GABRB3*) in its discovery stage[11]. There has not been any GWAS investigating people with PDD so far.

APOE: The *APOE* variants, especially its ε4 allele, are the most studied among all genetic variants in people with LBD[16-41]. Apolipoprotein-E (APOE) is involved in cholesterol mobilisation and redistribution during neuronal growth and injury[16], and it may promote β-

amyloid aggregation[16]. 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 18 positive studies and all four negative studies (Figure-2). We did not include three positive studies, because they did not provide allele frequency data. There was significant heterogeneity (χ^2=45.18, df=21; p=0.002) 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<0.001). Moreover, statistically significant associations with probable reduced risk of DLB[22] have been reported between *APOE*-ε2 and DLB[21-23,29]. Similarly, one of the studies investigating the association between *APOE*-ε3 and DLB has reported statistically significant reduced risk for DLB[29]. Furthermore, two moderate quality studies[32,42], and one poor quality study including PD controls without dementia (PDND)[43] 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[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[19,30,45-50]. We conducted a meta-analysis including data from the four positive studies and seven negative studies (Figure-3). There was significant heterogeneity (χ^2=29.22, df=11; p=0.002) 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=0.001).

GBA: The glucosylceramidase beta gene (*GBA*) encoding the lysosomal glucosylceramidase (GBA) enzyme has been consistently associated with PD[51,52]. *GBA* variants are likely to

increase the risk of earlier onset cognitive impairment in PD. Six studies[10,11,28,32,41,52] including four good quality studies have reported statistically significant associations between DLB and *GBA* variants including rs2230288[10], rs76763715[48], rs368060[32,52], rs35749011[11], and rs421016[28] (Table-2). Moreover, two studies have reported statistically significant associations between *GBA* variants and PDD[10,30] (Table-3).

SNCA: α-synuclein encoding *SNCA* variants rs974711[19], rs1348224[19] and rs7681440[11] have been associated with DLB. However, studies that investigated *SNCA* triplication[53], *SNCA* variant rs104893877[54] and variants in α-synuclein interacting protein encoding *SNCAIP*[55] did not find statistically significant associations with DLB. Moreover, *SNCA* variants rs10018362 and rs7689942[19] were significantly increased in PDD, and *SNCA* variants rs1372525, rs2583988, rs2619364, rs2619363 and rs2301135 were not significantly associated with PDD[56]. Apart from the replicated association between DLB and rs7681440[11], the reported genetic association findings between LBD and other *SNCA* variants have not been replicated so far.

MAPT**:** *MAPT* encodes tau protein. Two moderate[57,58] and one poor quality[59] studies have reported significant association between *MAPT* H1 haplotype and DLB, but two good quality studies have not replicated this finding[11,37]. Moreover, a moderate quality study has reported associations between PDD and *MAPT* H1 haplotype and another probably protective variant rs1467967[60].

Other genetic associations: Table-2 and Table-3 present other reported genetic associations of DLB, and PDD, respectively. The only GWAS has replicated the association between DLB and rs7314908 of *CNTN1*[11]. The reported genetic associations between DLB and rs897984 (*BCL7C*)[11], 2bp in exon 6 of *CHRFAM7A*[17], rs1426210 (*GABRB3*)[11], mtDNA haplogroup H[25], *SCARB2* variants[24] need further replication. Conflicting evidence exist for the genetic associations of DLB with other variants in *BCHE* (K allele)[33,61], *NOS2*[34,62], mtDNA[63],

PSEN1[26,64], *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*[27], *LRRK2*[69], *NOS3*[62], *PARK7*[70], *PRGN*[71], *RAB39B*[72], *SNCB*[73], *TFAM*[74] and *TF*[75] 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*[44] and *TREM2*[89] have reported negative findings.

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[90]. 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 (CNV) in people with DLB was also published in May 2019[91]. Five CNV regions including *ADGRG7*, *TFG*, *PDZD2*, *LAPTM4B*, *MSR1*, *NME1*, *NME2*, and *SPAG9* were reported to have genome-wide significant associations with DLB[91].

APOE-ε4 variant has the largest body of evidence in this topic[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[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[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 systematic studies investigating gene environment interactions in people with LBD. A recent genome-wide meta-analysis has identified 29 risk loci for AD[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[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[96], and the genes that are implicated in increased α-synuclein aggregation either directly (*SNCA, PSEN1*[97]) or indirectly (*MAPT*[57-60].) have been associated with LBD[98]. *SNCA* variants and *MAPT* H1subhaplotypes have been associated with increased tau fibrilization and deposition[59,60,99,100]. Potential interactions between these variants may lead to synergistic neurodegenerative effects of amyloid, tau and α-synuclein deposition[60,101]. 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 overexpression 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[115], and they may impair autophagy and clearance of misfolded proteins[116]. *CNTN1* encodes contactin 1 that modulates remyelination and neuroinflammation and regulates the activity of APP cleaving enzyme BACE1[11,117]. *NOS2* generates nitric oxide in neurons and microglia, and it promotes cell survival though inhibition of apoptosis[118]. Less *NOS2* CCTTT repeats leads to reduced level of nitric acid synthase that may increase oxidative stress, and may impair neuronal survival in LBD[38]. *ESR1* encodes oestrogen receptor alpha (ERα) that mediates the physiological effects of Estradiol-17-β including neuroprotective and antiapoptotic effects, especially survival of cholinergic neurons[119], modulating APP processing[119,120], and maintaining synaptic density[121]. It has been reported that Estradiol-17-β and *ESR1* activation may upregulate *APOE*-ε4 expression[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 *BCHE*-K variant results in nearly 30% less Butyrylcholinesterase activity[33] and it has been associated with reduced tau phosphorylation in people with dementia[123]. The *BCHE*-K variant has been found to be significantly less common among people with DLB[33]. Additionally, the reported genetic association between *CHRFAM7A* and LBD may highlight the importance of cholinergic system dysfunction in LBD[17,124]. *CHRFAM7A* is a duplicated gene complex including *CHRNA7* that encodes neuronal acetylcholine receptor subunit α-7 (nAChRα7). nAChRα7 has been implicated in the pathology of several neuropsychiatric disorders, and it is involved in memory, sensory information processing, and neuronal survival[125].

In comparison to 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[11,90]. None of the reported genetic asscoiations 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[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[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[127-130]. Future hypothesis-driven studies should prioritize 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.

Authors' 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.

Table 1: The studies that have reported statistically significant genetic association between *APOE*-ε4 and Dementia with Lewy Bodies.

Study	**Cases: Controls**	**ε4 allele numbers Cases: Controls**	**Odds Ratio (95% CI)**	**p value**
Harrington et al 1994[16]	‡26:58	19:17	4.56 (1.53-13.84)	p=0.003
Benjamin et al 1995[21]	‡28:46	20:14	3.10 (1.41-6.81)§	p=0.004
Lamb et al 1998[29]	49:101	35:29	3.31 (1.87-5.86)§	$p=6.25x10^{-5}$
Chinnery et al 2000[25]	84:179	No frequency data	NR	p<0.001 (1 ε4 allele) p=0.007 (2 ε4 alleles)
Xu et al 2000[34]	22:101	14:29	2.78 (1.32-5.87)§	p<0.05
Singleton et al 2002[31]	76:111	50:28	3.50 (2.1-5.9)	$p=5.6x10^{-6}$
Huckvale et al 2003[27]	53:720	48:202	5.07 (3.36-7.65)§	p<0.001
Akatsu et al 2004[20]	31:387	12:64	2.66 (1.35-5.26)§	p<0.005
Borroni et al 2006[23]	82:81	36:19	2.11 (1.15-3.87)	p=0.018
Feher et al 2009[17]	35:175	19:27	4.46 (2.31-8.60)§	p<0.0001
Feher et al 2009[18]	34:164	19:29	4.00 (2.08-7.68)§	p<0.0001
Meeus et al 2012[8]	99:626	49:193	1.81 (1.26-2.58)§	p<0.001
Tsuang et al 2013[35]	91:269	58:39	6.10 (3.5-10.5)	$p=1.2x10^{-16}$
Berge et al 2014[22]	156:643	100:185	5.90 (2.7-13.0)	p≤0.0005 (1 ε4 allele) p≤0.0005 (2 ε4 alleles)
Geiger et al 2016[26]	111:222	No frequency data	NR	p<0.001
Guella et al 2016[19]	922:971	620:318	2.50 (2.29-2.70)	p<0.002
Keogh et al 2016[41]	87:93	51:26	2.55 (1.51-4.32)§	p=0.0001
Vijayaraghavan et al 2016[33]	174:86	108:23	2.92 (1.78-4.78)§	p<0.001
Keogh et al 2017[28]	55:359	34:107	2.56 (1.62-4.02)§	p<0.001
Guerreiro et al 2018 (discovery)[11]	1216:3791	688:1061	2.40 (2.14-2.70)	$p=1.05x10^{-48}$
Guerreiro et al 2018 (replication)[11]	527:663	297:196		

‡: Cases were patients with SDLT (Senile dementia of Lewy body type); §: Odds ratios were calculated using the reported allele frequency data; NR: Not reported; NS: not significant.

Table 2: The studies that have reported other statistically significant genetic associations of Dementia with Lewy Bodies (DLB)

Study	Gene	Cases: Controls	Variant(s)	OR (95% CI)	p value
Vijayaraghavan et al 2016[33]	*BCHE*	174:86	One or two K alleles	0.49 (0.34-0.71)§	p<0.001†
Guerreiro et al 2018[11]	*BCL7C*	1743:4454	rs897984	0.74 (0.67-0.82)	$p=3.30x10^{-9}$
Feher et al 2009[17]	*CHRFAM7A*	35:175	2 bp deletion at 497–498 in exon 6	3.76 (2.21-6.39)§	p=0.001
Guerreiro et al 2018[11]	*CNTN1*	1743:4454	rs7314908	1.51 (1.27-1.79)	$p=2.32x10^{-6}$
Guerreiro et al 2018[11]	*GABRB3*	1743:4454	rs1426210	1.34 (1.21-1.48)	$p=2.62x10^{-8}$
Nalls et al 2013[10]	*GBA*	721:1962	"Mutations"	8.28 (4.78-14.88)	$p=5.52x10^{-15}$
Nalls et al 2013[10]	*GBA*	721:1962	rs2230288	2.72 (1.38-5.54)	p=0.006
Keogh et al 2016[41]	*GBA*	87:93	5 *GBA* variants	NR	p=0.043
Mata et al 2008[52]	*GBA*	57:554	rs76763715 or rs368060	10.00 (1.7-139.8)	p=0.045
Tsuang et al 2012[32]	*GBA*	79:391	"Pathogenic GBA mutation carriers"	7.60 (1.8-31.9)	p=0.001
Keogh et al 2017[28]	*GBA*	58:368	rs421016	NR	p=0.008
Guerreiro et al 2018[11]	*GBA*	1743:4454	rs35749011	2.55 (1.88-3.46)	$p=1.78x10^{-9}$
Labbe et al 2016[57]	*MAPT*	431:1049	H1G haplotypes	3.30 (1.34-8.12)	p=0.002
Labbe et al 2016[57]	*MAPT*	431:1049	H1L haplotypes	0.37 (0.15-0.92)	p=0.041
Labbe et al 2015[58]	*MAPT*	442:1679	rs143624519	5.76 (1.62-20.51)	p=0.007
Cervera-Carles et al 2016[59]	*MAPT*	51:325	H1 allele	1.81 (1.05-3.14)	p=0.032
Chinnery et al 2000[25]	mtDNA	84:179	Haplogroup H	NR	p=0.034
Xu et al 2000[34]	*NOS2*	22:101	(CCTTT)n repeat	5.04 (1.5-16.9)	p<0.01
Geiger at al 2016[26]	*PSEN1*	111:222	rs17125721	2.10 (1.04-3.76)	p=0.035
Guella et al 2016[19]	*SNCA*	922:971	rs974711	1.22 (1.07-1.38)	p<0.002
Guella et al 2016[19]	*SNCA*	922:971	rs1348224	0.74 (0.65-0.85)	p<0.002
Bras et al 2014[24]	*SNCA*	788:2624	Not specified	NR	$p=3.7x10^{-5}$
Guerreiro et al 2018[11]	*SNCA*	1743:4454	rs7691440	0.73 (0.66-0.81)	$p=6.39x10^{-10}$
Bras et al 2014[24]	*SCARB2*	788:2624	Not specified	NR	P<0.001
Keogh et al 2017[28]	*TREM2*	58:368	p.R62H	3.20 (1.7-27)	p=0.002

mtDNA: mitochondrial DNA; † higher K allele frequency in controls vs DLB case group; §: Odds ratios (OR) were calculated using the reported allele frequency data; NR: Not reported.

Table 3: The studies that have reported statistically significant genetic associations of Parkinson's Disease Dementia (PDD)

Study	**Gene**	**Cases: Controls**	**Variant(s)**	**OR (95% CI)**	**p value**
Sleegers et al 2004[78]	*A2M*	9 (LBD):283	D-allele	0.67 (0.23-1.96)§	p=0.009
Harhangi et al 2000[42]	*APOE*	26:4805	ε2, ε3, ε4	2.20 (1.7-2.9)	Significant†
Tsuang et al 2012[32]	*APOE*	81:269	ε2, ε3, ε4	3.10 (1.7-5.6)	$p=1.94x10^{-5}$ (ε4 allele)
Arai et al 1994[43]	*APOE*	14:49 (PDND)	ε2, ε3, ε4	4.68 (1.64-13.36)§	p<0.001
Lindqvist et al 2016[44]	*APOE*	55 (PDD) + 101 (DLB): 92 (PDND)	ε4	2.26 (1.18-4.34)	p<0.014
Isoe-Wada et al 1999[76]	*ESR1*	13:51 13:71 (PDND)	PvuII	2.81 (1.16-6.83)§ 3.34 (1.41-7.93)§	p<0.02 (PDD vs CTL) p=0.0073 (PDD vs PDND)
Nalls et al 2013[10]	*GBA*	151:1962	"Mutations"	6.48 (2.53-15.37)	$p=9.66x10^{-6}$
Nalls et al 2013[10]		151:1962	rs2230288	3.91 (1.41-10.86)	p=0.009
Meeus et al 2010[8]	*GBA*	75 (PDD) + 99 (DLB): 626	"Mutant alleles"	3.01 (1.25-7.20)§	p=0.010 (LBD vs CTL)
Seto-Salvia et al 2011[60]	*MAPT*	41(LBD):374	H1 haplotype	2.69 (1.47-4.95)	PDD: p=0.001
Seto-Salvia et al 2011[60]	*MAPT*	41(LBD):374	rs1467967	0.54 (0.34-0.85)	p=0.007‡
Guella et al 2016[19]	*SNCA*	198:971	rs10018362	1.77 (1.28-2.45)	p<0.002
Guella et al 2016[19]		198:971	rs7689942	2.10 (1.39-3.17)	p<0.002
Gatt et al 2013[74]	*TFAM*	63:1410	rs2306604	2.09 (1.13-3.89)	p=0.024 (AA genotype vs AG and GG)
Shibata et al 2012[79]	*UCHL1*	39:137	rs4861387	1.20 (0.58-2.50)§	p=0.03

CTL: controls (CTL); PDND: Parkinson's disease patients without dementia; †: p value has not been reported; ‡: decreased frequency in LBD ; §: Odds ratios (OR) were calculated using the reported allele frequency data.

Figure Legends

Figure-1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.

Figure-2: Meta-analysis of studies that have investigated the genetic association between *APOE*-ε4 and dementia with Lewy bodies.

Figure-3: Meta-analysis of studies that have investigated the genetic association between *APOE*-ε4 and Parkinson's disease dementia.

Supplementary information:

Supplementary table 1: The Q-Genie quality assessment scores of the included studies

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