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Title: Systematic review of gene expression studies in people with Lewy Body Dementia

Short running title: Gene expression changes in Lewy Body Dementia

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ABSTRACT

Objectives: Lewy body dementia (LBD) is the second most prevalent neurodegenerative dementia, and it causes more morbidity and mortality than Alzheimer's disease. Several genetic associations of LBD have been reported, and their functional implications remain uncertain. Hence, we aimed to do a systematic review of all gene expression studies that investigated people with LBD for improving our understanding of LBD molecular pathology and for facilitating discovery of novel biomarkers and therapeutic targets for LBD.

Methods: We systematically reviewed five online databases (PROSPERO protocol: CRD42017080647) and assessed the functional implications of all reported differentially expressed genes (DEG) using Ingenuity Pathway Analyses.

Results: We screened 3,809 articles and identified 31 eligible studies. 1,242 statistically significant ($p<0.05$) DEGs including 70 microRNAs have been reported in people with LBD. Expression levels of alternatively spliced transcripts of *SNCA, SNCB, PRKN, APP, RELA*, and *ATXN2* significantly differ in LBD. Several mitochondrial genes and genes involved in ubiquitin proteasome system and autophagy lysosomal pathway were significantly downregulated in LBD. Evidence supporting chronic neuroinflammation in LBD was inconsistent. Our functional analyses highlighted the importance of RNA-mediated gene silencing, neuregulin signalling, and neurotrophic factors in the molecular pathology of LBD.

Conclusions: α-synuclein aggregation, mitochondrial dysfunction, defects in molecular networks clearing misfolded proteins, and RNA-mediated gene silencing contribute to neurodegeneration in LBD. Larger longitudinal transcriptomic studies investigating biological fluids of people living with LBD are needed for molecular subtyping and staging of LBD. Diagnostic biomarker potential and therapeutic promise of identified DEGs warrant further research.

Keywords: Lewy body dementia, Parkinson's disease, systematic review, gene expression, RNA

Summations:

1. 1,242 differentially expressed genes including 70 microRNAs have been reported in people with LBD.
2. Several mitochondrial genes and genes involved in ubiquitin proteasome system and autophagy lysosomal pathway were significantly downregulated in people with LBD.
3. Our functional analyses highlighted the importance of RNA-mediated gene silencing, neuregulin signalling, and neurotrophic factors in LBD molecular pathology.

Considerations:

1. This systematic review has excluded studies that were not published in English. It did not include studies that investigated animal models or cell lines.
2. All included studies were small cross-sectional studies, and there was substantial heterogeneity among the included studies.
3. Majority of the included studies have employed relative quantification methods, so it was not possible to do combined analyses using their findings.

Introduction

Lewy Body Dementia (LBD) includes of two overlapping clinical syndromes, Dementia with Lewy Bodies (DLB) and Parkinson's Disease Dementia (PDD) (1). DLB is the second most common neurodegenerative dementia, and its incidence rate has been estimated as 112 per 100,000 for those over 65 (2,3). LBD leads to increased mortality (4), earlier nursing home admissions, more frequent falls, worse quality-of-life, higher costs (5) and more caregivers' burden than Alzheimer's disease (AD). DLB is underdiagnosed in many clinical settings, and nearly 50% of people with DLB reportedly remain misdiagnosed in the UK (6). Missing the diagnosis of LBD and treating associated neuropsychiatric symptoms with antipsychotic medications risk life threatening adverse effects such as neuroleptic malignant syndrome in people with LBD. Currently, we do not have a reliable biological fluid based diagnostic biomarker or a disease modifying drug for LBD. Improving our knowledge of molecular mechanisms underlying neurodegeneration in LBD is essential for discovering reliable diagnostic biomarkers and novel therapeutic targets for LBD (3,7).

Although the onset of most LBD appear sporadic, several studies have reported familial aggregation of LBD and its core clinical features (8,9). The heritability of DLB has been estimated as 59.9%, and the genetic risk factors for DLB are likely to be independent from known risk variants of AD and Parkinson's disease (PD) (10). Two genome wide association studies (GWAS) (11,12) and a genome wide analysis of copy number variants (13) have investigated the genetic associations of DLB. There has not been any specific GWAS investigating people with PDD. Genetic associations between LBD and the variants in *APOE, GBA, SNCA* and *MAPT* have been replicated by two or more studies. Other reported genetic associations of LBD that need further replication include the variants in *ADGRG7*, *BCHE-K, BCL7C, CHRFAM7A, CNTN1, GABRB3, LAPTM4B*, mtDNA*, MSR1*, *NME1*, *NME2*, *NOS2A, PDZD2*, *PSEN1*, *SCARB2, SPAG9, TFG*, *TREM2*, *UCHL1*, and *ZFPM1*.

Genetic association studies cannot clarify the functional implications of the identified genetic associations. Gene expression studies investigating Ribonucleic acid (RNA) levels (14) are necessary for quantifying transcriptional changes and for understanding the effects of gene expression regulation and alternative splicing. Unlike genetic associations, gene expression changes are dynamic and tissue specific. As gene expression differs with disease progression, gene expression studies help staging diseases and identifying RNA-based therapeutic targets (15). Gene expression studies in people with LBD have highlighted the importance of alternative splicing of α-synuclein in the molecular pathogenesis of LBD. Increased expression of α-synuclein-112, and decreased expression of α-synuclein-126 in the post-mortem frontal cortices of people with LBD have been reported (16). Gene expression profiling of post-mortem LBD brains and biological fluids of people living with LBD can advance our molecular level mechanistic understanding of neurodegeneration in LBD. This will facilitate identifying reliable diagnostic biomarkers and novel therapeutic targets for LBD. Considering the need for a comprehensive summary of all available evidence from the gene expression studies in people with LBD, we aimed to conduct the first systematic review on this topic.

Materials and Methods

Study design: The protocol for this systematic review has been registered in the international prospective register of systematic reviews (PROSPERO protocol CRD42017080647; available at http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080647).

Search strategy: We systematically searched the following five online databases: MEDLINE/PubMed (since 1946), EMBASE (since 1974), PsycINFO (since 1806), Web of Science (since 1900), and OpenGrey (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 express*) OR (RNA) OR (qPCR) OR (RNA AND Seq*). Reference lists of the studies included in the review were explored for identifying other potentially eligible studies. All studies that were published on or before 1st January 2018 were considered. Studies that were not published in English were not included.

Eligibility criteria: We included all gene expression studies that satisfied the following eligibility criteria, i) They were human studies. Studies on animal models and *in vitro* studies investigating human tissue derived cell lines were excluded, ii) They presented original research data, iii) Participants in at least one study group were clinically diagnosed to have DLB or PDD or LBD. Studies that solely included people with other types of dementia or PD without dementia were excluded, iv) There was a control group in which LBD was clinically ruled out, v) They investigated expression levels of at least one gene.

Study selection: We merged our search results across the databases and removed duplicates using the RefWorks software (ProQuest LLC, USA). We excluded the abstracts that did not mention investigating gene expression changes in people with LBD. We attempted retrieving full texts of all potentially eligible abstracts and assessed the eligibility of the full-text papers. The studies that failed to meet one or more of the eligibility criteria were excluded. When a conference abstract was not accompanied by its full text, 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.

Quality assessment: We assessed the quality of eligible studies using a tool (Supplementary information table-1), adapted from the Quality of genetic association studies tool (Q-Genie) (17,18). The tool assessed the following 11 dimensions, (i) the rationale for study, (ii) selection and definition of people with LBD, (iii) selection and comparability of comparison groups, (iv) technical assessment of gene expression, (v) non-technical aspects of assessment of gene expression, (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) testing of assumptions and inferences for gene expression analyses, and (xi) appropriate interpretation of the study results. Each dimension was scored on a scale from one (poor) to seven (excellent), so the total scores could range from 11 to 77.

Data extraction: We extracted the following data, i) population characteristics including their mean age, ethnicity, and severity of illness (ii) sample size in each study group, iii) case definition, iv) investigated genes and their transcripts, v) investigated tissue, vi) methods for analysing gene expression changes, vii) differential fold changes between the study groups with their p-values, viii) statistical correction for multiple testing, ix) statistical analyses addressing the effects of potential confounders.

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 reported gene expression changes in post-mortem brain tissue and in biological fluids of people with DLB or PDD. We have summarised the reported findings on alternative splicing and on differentially expressed microRNA (miRNA) in people with DLB or PDD separately.

Data analyses: Functional implications of identified differentially expressed genes (DEGs) ($p<0.05$) were analysed by the ingenuity pathway analyses (IPA) using the Ingenuity knowledge base (Ingenuity, Redwood City, USA). IPA is a powerful functional analysis tool that helps identifying potential biomarkers within the context of biological systems. Our IPA analysis settings included stringent filters with only experimentally observed relationships, and we identified disrupted functional pathways and dysfunctional molecular networks after Benjamani-Hochberg false discovery rate (FDR) at 5% correction in people with LBD.

Results

Included studies: Figure-1 presents the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (19) flow chart describing the process of identifying all eligible studies. We identified and screened 2,379 papers after removing the duplicates and found 31 papers eligible to be included in this systematic review. Among the 31 included studies, 23 measured gene expression changes using quantitative polymerase chain reactions (qPCR). There were three studies using gene expression microarrays (20-22) and three studies using next-generation RNA sequencing (RNA-Seq) (23-25). One study employed northern blotting (26), and another used RNAse protection assay (27). Supplementary information table-2 presents the quality assessment scores of all included studies. Their quality assessment total scores ranged from 40 to 56 (median=49), and there were 23 studies with quality assessment total scores above 45.

Overall, 369 individual people with LBD and 368 controls were included in these 31 studies. Among them, there were 294 people with DLB and 75 people with PDD. Most of the studies have investigated post-mortem brain tissue, obtained from various brain banks. Investigated regions of brain tissue include frontal cortex, temporal cortex, motor cortex, medial temporal gyrus, superior parietal gyrus, superior frontal gyrus, substantia nigra, hippocampus, anterior cingulate cortex, locus coeruleus, caudate nucleus and pons. All but one study have reported the details of brain bank, and the investigated region of brain tissue. There were only three studies (26,28,29) that have investigated peripheral blood samples, and there was only one study (30) that has investigated cerebrospinal fluid (CSF). Supplementary information table-3 presents the list of all 1,242 reported DEGs in people with DLB. There were 1,236 reported DEGs in post-mortem brain tissue, and six DEGs in biological fluids have been reported so far.

DEGs in post-mortem DLB brains*:* Table-1 presents a summary of studies that have investigated gene expression changes in post-mortem DLB brains. α-synuclein encoding *SNCA* total gene expression levels did not differ significantly in people with DLB, but its shorter isoforms have been found to be significantly upregulated. Reported DEGs in post-mortem DLB brains included genes involved in protein signalling, folding and degradation. *UCHL-1* encoding ubiquitin C-terminal hydrolase L1, *SNCAIP* encoding synphilin-1, and *PRKN* encoding Parkin contribute to the ubiquitin proteasome system (UPS) that is essential for the regulation and removal of misfolded proteins. Statistically significant downregulation of *UCHL-1* and *PRKN* and significant upregulation of *SNCAIP* have been reported in DLB brains (31-33). The autophagy lysosomal pathway (ALP) is crucial for protein degradation (34). *GBA* gene encoding lysosomal enzyme beta-glucocerebrosidase was significantly downregulated in DLB brains (35). β-site amyloid precursor protein (APP) cleaving enzyme encoding *BACE1* was found to be significantly upregulated in DLB (36). Moreover, genes involved in synaptic regulation and neurotransmission such as *TH, ADRA2C* and *ADRA1D* were significantly differentially expressed in post-mortem DLB brains, but these findings have not been replicated so far (37). Furthermore, *HSP*70 and *HSP*27 were found to be upregulated up to three-fold in DLB brains (38,39).

DEGs in post-mortem PDD brains*:* Six studies have investigated gene expression changes in post-mortem PDD brains (21,24,25,27,40,41) (Table-2). A RNA-Seq study that investigated the posterior cingulate cortical transcriptomics of people with PDD has reported statistically significant upregulation of genes associated with protein folding pathways such as *HSP40* and *DNAJB1*, and downregulation of genes associated with hormonal activity, ion transport, nerve growth and cytoskeleton structure (24). Inflammation associated *CSF3* and *SELE* were significantly upregulated, and *PENK*, *CRH,* and *SST* were significantly downregulated in people with PDD (24). Another study that investigated the gene expression changes in posterior

cingulate cortices of people with PDD using gene expression microarrays identified 556 DEGs ($p<0.01$) in PDD. There was downregulation of genes involved in neurite growth and cell adhesion such as *KIF21A*, *DYNC2LI1* and *TBCA* (21). Another study that employed RNAse protection assay has reported significant upregulation of G protein-coupled receptor (GPCR) pathways related *ARRB2* ($p<0.001$), *ARR3* ($p<0.001$), *GRK3* ($p<0.01$) and *GRK5* ($p<0.05$) in post-mortem PDD brains (27).

DEGs in biological fluids of people with LBD*:* There were only three studies which have investigated gene expression changes in biological fluids of people with DLB. Two of them have investigated peripheral leukocytes (28,29), and the third has investigated CSF (30). There was only one study that specifically investigated gene expression changes in biological fluids of people with PDD (26). *SNCA* total gene expression levels did not differ significantly, but its isoform *SNCA*-126 level was significantly upregulated in peripheral leukocytes of people with DLB (29). Another study has assessed expression levels of 11 mitochondrial genes in peripheral leukocytes, and found significant ($p<0.05$) downregulation of *MT-ATP8, MT-CO2, MT-CO3* and *MT-ND2* in people with DLB (28). Only *MIR-125B* was significantly downregulated in CSF of people with DLB ($p=0.03$) (30). Moreover, expression levels of *HSP70* did not differ significantly in peripheral mononuclear blood cells of people with PDD (26).

Potential miRNA biomarkers for LBD*:* Four studies have reported differential expression of miRNAs in people with DLB (22,23,30,42), and two more have investigated differentially expressed miRNAs in people with PDD (24,25). 70 differentially expressed miRNA in people with LBD have been identified so far (Table-3) (Supplementary information table-3). *MIR-125B* was significantly differentially expressed in both post-mortem DLB temporal cortices and CSF of people living with DLB (30,42). Differential expression levels of 36 miRNAs in prefrontal cortices could distinguish PDD from PD with 81.2% sensitivity and 88.9%

specificity (25). Moreover, a study that investigated anterior cingulate cortices of people with DLB using RNA-Seq has identified 14 potential upstream regulatory miRNAs after appropriate multiple testing correction (23) (Table-3).

Importance of alternative splicing in LBD: Expression levels of multiple isoforms of *SNCA, SNCB, PRKN,* and *APP* have been evaluated in people with DLB. Four alternatively spliced transcripts of *SNCA, SNCA*-98*, SNCA*-112*, SNCA*-126*,* and *SNCA*-140, have been studied. *SNCA*-98 was expressed 2.7 times more in frontal cortices of people with DLB ($p<0.05$) (43). Similarly, *SNCA*-112 expression levels were upregulated in people with DLB by twofold, when compared with controls without cognitive impairment ($p=0.002$), and by threefold, when compared with people with AD ($p<0.001$). Four-fold downregulation ($p<0.001$) in frontal cortices, and two-fold upregulation in peripheral leukocytes of *SNCA*-126 in people with DLB have been reported (16,29). Significant ($p=0.008$) downregulation of *SNCA*-140 in DLB brains (44) has been reported, but another study has failed to replicate this finding in frontal cortices and caudate nuclei of people with DLB (41). Upregulation of *SNCA*-140 levels in temporal cortices, and its downregulation in caudate nuclei of people with PDD has been reported (40). Two transcript variants (TV) of *SNCB* have been investigated in people with LBD (41,45). Expression levels the alternatively spliced isoforms, *SNCB*-TV1 and TV2, varied across different brain regions. *SNCB*-TV1 and TV2 were significantly downregulated in temporal and frontal cortices, and *SNCB*-TV1 was significantly upregulated in caudate nuclei of people with DLB. *SNCB*-TV1 and TV2 were significantly upregulated in temporal cortices and caudate nuclei of people with PDD (40,41). Levels of both *SNCB* transcripts were significantly reduced in pons of people with PDD (40).

Three major isoforms of *APP*, *APP*-695, *APP*-751, and *APP*-770 have been investigated in people with DLB. People with DLB had significantly higher levels of *APP*-770 ($p<0.05$) and significantly lower levels of *APP*-695. Results on *APP*-751 expression levels

were inconsistent (46,47). Moreover, significantly (p=0.02) lower levels of *PRKN*-TV7 has been reported in people with DLB (48). Furthermore, another study has investigated the importance of alternative splicing in posterior cingulate cortices of people with PDD using RNA-Seq and SpliceSeq (49) software (24). There was 2.6 fold overexpression of alternatively spliced isoforms of *RELA,* compared to its main transcript, in people with PDD. More than threefold downregulation of alternatively spliced isoforms of *ATXN2* in PDD was found (24).

Functional analyses of reported DEGs in LBD: We investigated the functional implications of the 1,242 reported DEGs ($p<0.05$) using IPA. Movement disorders ($p=2.42X10^{-9}$), disorders of basal ganglia ($p=2.71X10^{-9}$), schizophrenia ($p=3.29X10^{-8}$), immune response of brain ($p=3.48X10^{-7}$), neuronal death and survival ($p=7.34X10^{-6}$), tauopathy of hippocampus ($p=2.96X10^{-5}$), neuronal morphology ($p=4.28X10^{-5}$), synaptic transmission ($p=3.93X10^{-4}$), and tauopathy of amygdala ($p=4.02X10^{-4}$) associated genes were significantly enriched among the reported DEGs in people with LBD. Figure-2A presents the molecular pathways that were significantly enriched among the LBD DEGs after Benjamini-Hochberg false discovery rate (FDR) correction at 5%. Initiation of protein translation related EIF2 signalling, neuronal maintenance related neuregulin signalling, oxidative damage, apoptosis, and neuronal survival related PEDF signalling, signal transduction via phosphorylation and cell survival related mTOR signalling, and gene transcription regulating HMGB1 signalling pathways associated genes were significantly enriched among the LBD DEGs after FDR correction (Supplementary information table-4). The genes, associated with neuroinflammation signalling pathway, were significantly enriched among LBD DEGs after FDR correction, and they included 21 upregulated and 14 downregulated DEGs. Moreover, movement of myeloid cells related genes were significantly enriched among the downregulated LBD DEGs ($z=-2.24$; $p=3.23X10^{-4}$).

Our IPA upstream analyses and causal network analyses revealed that inhibition of *TCF7L2* encoding a transcription factor ($p=4.44X10^{-21}$) and of neurotrophic *BDNF*

($p=7.39X10^{-6}$) were likely upstream biological causes leading to the reported gene expression changes in people with LBD (50). Furthermore, they highlighted the importance of RNA-mediated gene silencing in the molecular pathology of LBD. *AGO2* ($p=2.22X10^{-8}$) encoding protein argonaute-2 that is essential for the formation RNA-induced silencing complex (RISC), and *DICER1* (p=7.57X10-6) encoding dicer that cleaves miRNA and small interfering RNA (siRNA) and activates RISC were identified as potential upstream biological causes for the reported gene expression changes in LBD. Our IPA network analyses (Supplementary information table-5) showed that several reported DEGs in LBD including *APBA2*, *HTRA2*, *ENO2*, and *MIR17* directly or indirectly interact with APP and Tau encoding *APP* and *MAPT* (Figure-2B). This dysfunctional molecular network can explain neurodegeneration in LBD and varying degrees of comorbid AD pathology, reported in many post-mortem LBD brains (Figure-2B). PD and DLB associated genes, *GBA*, *PRKN*, and *SCARB2*, directly interact with *SNCA* that interacts with L-3,4-dihydroxyphenylalanine (L-DOPA) synthesising Tyrosine Hydroxylase gene (*TH*) and with *PSEN1* encoding an essential protein for γ-secretase complex that cleaves β-amyloid from APP. Reported downregulation of *PSEN1* can increase α-synuclein aggregation independent of its γ-secretase activity, and associated downregulation of *SNCB* further increases α-synuclein aggregation that leads to formation of Lewy bodies (51). Figure-2C presents a dysfunctional molecular network including differential expression of these genes and their interactions. Figure-2D presents the complex interactions between neurotrophic *BDNF* and RNA-mediated gene silencing, regulated by *DICER1*, *AGO2*, and associated miRNAs. This dysfunctional molecular network can influence gene expression of many downstream genes and can impact neuronal survival and maintenance in people with LBD.

Discussion

This is the first systematic review of all gene expression studies that have investigated people with LBD. We have listed all reported DEGs in people with LBD and have investigated their functional implications. Our functional analyses advance our understanding of molecular mechanisms underlying neurodegeneration in LBD. The strengths of this systematic review include its broad eligibility criteria, following PRISMA guidelines, and searching multiple databases including grey literature. Its limitations are excluding studies that were not published in English, not including studies that investigated animal models or cell lines, and substantial heterogeneity among the included studies. All included studies were small, and the smallest study has included only four people with LBD (42). The studies have not reported sample size estimation or power analysis, so type-II error is likely. They differed widely on their population characteristics, case definitions, selection of controls, methods for measuring gene expression changes, and statistical analyses. Many studies did not employ statistical corrections for multiple testing. Majority of the studies have employed relative quantification qPCR, so it was not possible to do combined analyses using their findings. Moreover, another RNA-Seq study that investigated anterior cingulate and dorsolateral prefrontal cortical transcriptomics of people with DLB and PDD was published after the completion of this systematic review in June 2019 (52). It identified 12 genome-wide significant DEGs (*MPO*, *SELE*, *CTSG*, *ALPI*, *ABCA13*, *GALNT6*, *SST*, *RBM3*, *CSF3*, *SLC4A1*, *OXTR*, and *RAB44*) in people with LBD.

Although α-synuclein aggregation is the key initial step in the formation of Lewy bodies (53), α-synuclein encoding *SNCA* total gene expression levels often do not differ significantly in people with LBD. Two of its alternatively spliced shorter isoforms, *SNCA*-98 and *SNCA*-112, have increased propensity for aggregation (16), and they were found to be significantly upregulated in DLB brains (43). This highlights the need for further in-depth investigation of RNA biology, alternative splicing, and expression levels of individual transcripts in people

with LBD and other α-synucleinopathies (54). Upregulation of *SNCA*-126 could be detected in peripheral leukocytes of people living with DLB (29), and diagnostic biomarker potential of peripheral levels of *SNCA* transcripts warrant further research. Moreover, alternative splicing of β-synuclein encoding *SNCB* also plays an important role in the pathology of α-synucleinopathies (55). β-synuclein prevents α-synuclein inhibiting proteasomes, and it inhibits further α-synuclein aggregation (45). Expression levels of the two *SNCB* transcripts differ between DLB brains with and without co-existent AD pathology (41). *SNCB*-TV1 and TV2 were significantly downregulated in temporal cortices of people with DLB, and they were significantly upregulated in temporal cortices of people with PDD (40,41). Further investigation of expression levels of individual transcripts of *SNCB* may lead to molecular subtyping of LBD (41).

Lewy bodies are complex structures, and they are made of more than 80 distinct proteins (56). Available gene expression findings in people with LBD highlight the defects in molecular networks clearing abnormal proteins than overexpression of a few pathogenic genes. Optimal functioning of ALP and UPS is essential for the degradation of misfolded proteins (57). Prior studies, which mainly focussed on expression levels of genes associated with AD or PD, have indicated dysfunctional ALP and UPS contributing to neurodegeneration in LBD. They have reported statistically significant downregulation of *UCHL-1*, *PRKN*, and *GBA* in people with LBD (31-33,35). Recent transcriptomic studies have advanced our understanding of dysfunctional molecular networks involving ALP and UPS in people with LBD (20-25,52). Decreased expression of *GBA* impairs lysosomal protein degradation and leads to α-synuclein aggregation and neurotoxicity in stem cell derived neurons (58). Aggregated α-synuclein can set off a vicious cycle by inhibiting neuronal lysosomal activity further (58). *SCARB2* encodes a lysosomal membrane protein that transports GBA to lysosomes (59), and its downregulation may impair the ALP further in people with LBD. *GBA*, *PRKN*, and *SCARB2* directly interact

with *SNCA* and they interact indirectly with *TH*, *SNCB*, and *PSEN1*. This dysfunctional network and the decreased expression of *UCHL1* that is essential for the hydrolysis of misfolded proteins by neuronal UPS (60,61) exacerbate α-synuclein aggregation and cytoplasmic accumulation of other misfolded proteins.

Significantly decreased expression levels of mitochondrial genes involved in energy metabolism have been reported in people with LBD. Significant downregulation of *MT-ATP8, MT-CO2, MT-CO3* and *MT-ND2* could be measured in peripheral leukocytes of people with DLB (28). Reduced levels of mitochondrial complex I activity and oxygen uptake in DLB brains have been reported (62,63). Moreover, prior genetic association studies have found significant associations of LBD with mtDNA haplogroup H (64) and *TFAM* encoding mitochondrial transcription factor A (65). A recent RNA-Seq study and subsequent analysis of metabolic reprogramming in LBD brains by genome scale metabolic modeling (66) have highlighted the importance of mitochondrial dysfunction in LBD pathology (52). Mitochondrial dysfunction may set off a vicious cycle by generating more reactive oxygen species, which can lead to more mitochondrial oxidative damage (67). Reactive oxygen species and consequent oxidative stress lead to α-synuclein aggregation that in turn impair more mitochondria (67). Further studies are warranted for investigating associated molecular mechanisms as well as the biomarker and therapeutic potential of mitochondrial transcripts in LBD.

Our functional analyses of reported DEGs highlighted the importance of RNA-mediated gene silencing, neuregulin signalling, downregulation of neurotrophic factors in the molecular pathology of LBD. Downstream regulatory effects of decreased expression of neurotrophic *BDNF* may explain many reported gene expression changes in people with LBD (50). *BDNF* interacts with *AGO2* and *DICER1*, which were found to be upregulated in people with LBD. *AGO2* is essential for the formation of RISC and *DICER1* is important for the

activation of RISC. Consequent RNA-mediated gene silencing may lead to downregulation of several downstream genes, related to neuronal survival and maintenance in people with LBD. Moreover, several reported DEGs in LBD interact with *APP* and *MAPT*. *BACE1* expression levels were significantly upregulated in people with DLB (36), and there is a two-way relationship between α-synuclein aggregation and β-amyloid secretion (68). These findings may explain varying degrees of co-existent amyloid and Tau pathology in people with LBD.

Unlike AD (69), available gene expression studies have provided inconsistent evidence for the presence of chronic neuroinflammation in people with LBD. Inflammation associated genes were significantly upregulated in people with PDD (21). However, a gene expression microarray study and a RNA-Seq study have documented statistically significant downregulation of several inflammation associated genes including *IL1B*, *IL2*, *IL6*, *CXCL2*, *CXCL3*, *CXCL8*, *CXCL10*, and *CXCL11* in post-mortem DLB brains (20,52). *TNF* was upregulated only in rapidly progressive DLB (70), and another study has found upregulation of *IL6* in hippocampi of people with DLB (n=5) (71). However, these findings have not been replicated. Moreover, a recent transcriptomic and proteomic study has reported lack of evidence for microglia mediated neuroinflammation in post-mortem pulvinar of people with DLB (72). Optimal microglial activation is essential for neuronal survival and synaptic plasticity (73). Decreased expression of inflammation associated genes leading to impaired neuronal survival rather than chronic neuroinflammation may explain neurodegeneration in DLB (52). The differential expression levels of inflammation associated genes may help distinguishing DLB from PDD and AD, and their diagnostic and prognostic biomarker potential warrant further research.

Each neurodegenerative disorder is hypothesised to have its own unique peripheral miRNA signature (74). We have listed 70 miRNA that were found to be differentially expressed in people with LBD, and their biomarker and therapeutic potential need further

investigation. Identifying differentially expressed miRNA in post-mortem LBD brains advances our molecular level mechanistic understanding. However, discovery of clinically adoptable diagnostic biomarkers requires identifying differentially expressed miRNA in biological fluids of people living with LBD (30). Despite their vulnerability for degradation, RNA, especially miRNA, remain stable in biological fluids by being either bound to protein complexes or encapsulated within blood cells or extracellular vesicles (EV) (75). Only one study has evaluated miRNA expression changes in biological fluids of people with LBD (30), and there has not been any systematic research investigating the EV RNA expression levels in people with LBD. CSF small EVs can transmit α-synuclein aggregation in-vitro (76). Small EVs can cross blood brain barrier (77), and they transport RNA between brain and peripheral circulation. Diagnostic biomarker potential of small EV RNA, enriched for neuronal origin, is increasingly recognised (78,79), and the need for more studies investigating small EV RNA in people with LBD cannot be overemphasised.

Notwithstanding the extent of research on gene expression changes in people with PD without dementia, there is a scarcity of studies investigating these changes in people with PDD. The nosological validity of DLB and the diagnostic boundaries between DLB and PDD continue to be debatable, because the clinical presentations of advanced stages of DLB and PDD are often identical (80). Prevailing sparse evidence that comes almost exclusively from post-mortem brain tissue of people with clinically advanced PDD have indicated limited overlap between DEGs in DLB and PDD. Transcriptomes of DLB and PDD may display more pronounced differences during earlier clinical stages. We suggest more transcriptomic studies investigating biological fluids of people living with DLB and PDD for advancing our understanding of molecular differences between these two clinically overlapping disorders. All studies, included in this systematic review, have expressed gene expression changes at only one point of time. Gene expression changes are dynamic, and they differ with disease

progression, so we suggest future gene expression studies investigating the longitudinal gene expression changes in biological fluids of people living with LBD.

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Authors' contributions:

APR conceived this study, and both APR and AC designed the systematic review protocol. AC reviewed the literature, identified eligible studies, and completed necessary quality assessment and data extraction. AC and APR interpreted the findings of the included studies. APR performed the Ingenuity Pathway Analyses. AC wrote the initial draft. Both authors were involved in further critical revisions of the manuscript, and they have approved the final version of the manuscript.

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Statement of interest:

Both authors declare that they do not have any competing interests.

Figure legends

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

Figure-2: Functional analyses of reported differentially expressed genes (DEG) in people with Lewy Body Dementia (LBD)

2.A. Canonical pathways that were enriched among the reported DEG in people with LBD. Green represents downregulated genes, and red represents upregulated genes. Yellow line presents the p-values after Benjamini-Hochberg false discovery rate (5%) correction.

2.B. A dysfunctional network of reported DEG may lead to amyloidopathy and tauopathy in LBD.

2.C. A dysfunctional molecular network involving α-synuclein, presenilin 1, and tyrosine hydroxylase may explain α-synuclein aggregation and neurodegeneration in LBD.

2.D. A dysfunctional molecular network involving brain derived neurotrophic factor, dicer 1, and argonaute highlights the importance of neurotropic factors and RNA silencing complexes in the pathophysiology of LBD.

2.(B-D). Green represents downregulated genes, and red represents upregulated genes. Solid lines represent direct interactions and dotted lines represent indirect interactions.

Supplementary information:

Supplementary information 1: A tool for quality assessment of gene expression studies. This tool has been adapted from the quality of genetic studies (Q-Genie) tool.

Supplementary Information 2: Quality assessment scores of the studies included in this systematic review.

Supplementary Information 3: A list of genes that have been reported to be significantly differentially expressed in people with Lewy Body Dementia.

Supplementary Information 4: Canonical pathway analysis of reported differentially expressed genes in people with Lewy Body Dementia.

Supplementary Information 5: Network analysis of reported differentially expressed genes in people with Lewy Body Dementia.

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