Advances in the Genetics and Pathology of Lewy Body Dementia

Sonja W. Scholz, MD[1,2], Njideka U. Okubadejo, MD[3], Priya Prakash, PhD[4], Shane A. Liddelow, PhD[4,5,6], Mina Ryten, MD[7], Glenda M. Halliday, PhD[8,9]

1. Neurodegenerative Diseases Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA
2. Department of Neurology, Johns Hopkins University Medical Center, Baltimore, MD, USA
3. Neurology Unit, Department of Medicine, Faculty of Clinical Sciences, College of Medicine, University of Lagos, Lagos, Nigeria
4. Institute for Translational Neuroscience, NYU Grossman School of Medicine, New York, New York, USA
5. Department of Neuroscience, NYU Grossman School of Medicine, New York, New York, USA
6. Department of Ophthalmology, NYU Grossman School of Medicine, New York, New York, USA
7. UK Research Institute, Cambridge University, Cambridge, UK
8. The University of Sydney Brain and Mind Centre & Faculty of Medicine and Health School of Medical Sciences, Sydney, NSW 2050, Australia
9. Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD, 20815, USA

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Corresponding author:
Sonja W. Scholz, MD, PhD
Neurodegenerative Diseases Research Section
National Institute of Neurological Disorders and Stroke
National Institutes of Health
35 Convent Drive, Room 1B-205
Bethesda, MD 20892, USA
Email: sonja.scholz@nih.gov
Phone number: +1 (301) 496-0013

Lewy body dementia is a heterogeneous disease that is underdiagnosed and poorly understood. Pathologically, Lewy body dementia is characterized by the accumulation of intraneuronal aggregates of misfolded α-synuclein, known as Lewy bodies and Lewy neurites. The genetic architecture of Lewy body dementia is complex, involving both common genetic variants with small risk effects and rare genetic variants with large effects. Alzheimer's disease pathology frequently coexists with Lewy body pathology and influences the clinical presentation. A deeper understanding of the pathophysiological pathways, including mitochondrial dysfunction, lysosomal dysfunction, and neuroinflammation, can enhance disease modeling, and this knowledge will ultimately facilitate the development of therapeutic interventions. The biological relationships that Lewy body dementia shares with other neurodegenerative and psychiatric disorders may also prove crucial for the development of therapeutic strategies.

1. INTRODUCTION

Lewy body dementia (LBD) is the second most prevalent neurodegenerative form of dementia in people aged 65 and older after Alzheimer's disease. It manifests with varying signs and symptoms that can present in combination, such as fluctuating attention, parkinsonism, visual hallucinations, and rapid eye movement (REM) sleep behavior disorder.[1] Additional clinical features, such as dysautonomia and mood disorders**,** can contribute to the heterogeneity in presentation in people with the condition.[1] Its defining pathological hallmark is the neuronal cytoplasmic deposition of misfolded α-synuclein protein. These protein deposits, called Lewy bodies, are also present in postmortem neuropathological analyses of most patients with Parkinson's disease, and the two conditions are collectively classified as Lewy body diseases. LBD is an umbrella term encompassing two clinical syndromes, Parkinson's Disease Dementia and Dementia with Lewy Bodies.

Parkinson's Disease Dementia and Dementia with Lewy Bodies are clinically distinguished on the basis of the time of motor symptom onset relative to developing dementia, following the "1-year rule", an arbitrary but pragmatic consensus tool for splitting the disease continuum into the two entities.[2] In Parkinson's Disease Dementia, motor symptoms precede dementia by at least one year, while persons with Dementia with Lewy Bodies manifest with dementia before or within one year of motor symptom onset. However, people with Parkinson's Disease Dementia and Dementia with Lewy Bodies are neuropathologically indistinguishable in terms of their Lewy pathology, and their clinical presentations are considered to exist on a disease spectrum.

This article is the first in a three-part Series covering recent advancements in Dementia with Lewy Bodies. In this first article, we discuss advances in molecular understanding based on genetic and pathological insights. We also cover new evidence on the Lewy body dementia continuum.

2. EPIDEMIOLOGY

The median age at diagnosis for patients with LBD is 76 years, with initial signs and symptoms usually appearing at age 50 years or older.[3] Men have a higher incidence than women, particularly after the age of 60 (Panel 1).[3] LBD is often misdiagnosed as a psychiatric disorder or another form of dementia, at least initially, leading to delays in establishing the diagnosis. This underdiagnosis hinders accurate epidemiological measurements.[4,5] Nonetheless, population-based studies report an incidence between 3.6 and 5.9 per 100,000 person-years,[3,6,7] rising to 77.1 per 100,000 person-years for the older population (80–99 years).[3] Median survival is 5 to 8 years from the time of diagnosis[8,9] and is typically shorter than the life expectancy observed among patients diagnosed with Alzheimer's disease.[9,10]

Extrapolating from these data, researchers estimate LBD accounts for 20–30% of all dementia cases,[8,11] and the disease affects about 1.4 million people in the United States.[12] This large number of cases places an enormous burden on healthcare systems and communities.[13] The expenditure is magnified by the high cost of caring for LBD patients due to the complex nature of the disease and the multidisciplinary care

requirements.[14,15] The treatment options are limited to symptomatic therapies, highlighting the need to advance our understanding of LBD's pathobiology.

3. GENETICS OF LEWY BODY DEMENTIA

While LBD is predominantly a sporadic, clinically heterogeneous condition of late adulthood, the description of rare familial presentations and the fact that siblings of Dementia with Lewy Bodies patients have a two-fold risk of developing the disease underscore the significant role of genetic factors in the disease (Figure 1).[16-20]

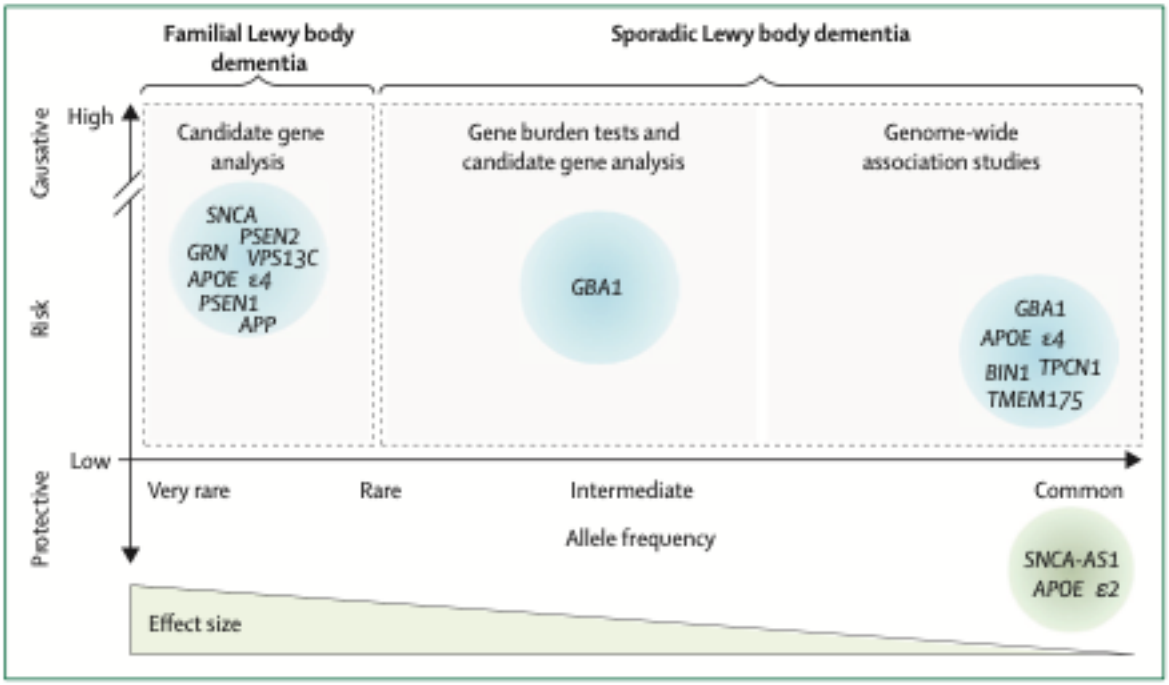

Figure 1: **The complex genetic architecture of Lewy body dementia**

Genomic studies have enhanced our understanding of the genetic architecture of LBD. The field has also greatly benefited from research insights derived from related neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease. Recently, the direct application of genome-wide association studies (GWAS), whole genome sequencing, and other modern complex genetic approaches to large LBD case-control cohorts has unveiled crucial insights into the genetic risk factors and pathways of disease susceptibility. Familial aggregation, twin, and heritability studies indicate a significant genetic component (18% for twin studies,[21] 11% for whole genome sequencing studies[22]). However, current knowledge has only explained a small fraction of the measured heritability, indicating that much work remains to be done.[22]

Insights from Parkinson's Disease Genetics

Missense and copy number mutations in the *SNCA* gene on chromosome 4q22.1, which encodes α-synuclein, have been identified as a rare cause of familial, autosomal dominantly inherited Parkinson's disease.[23] Researchers quickly noticed that patients

with pathogenic mutations in *SNCA* often show prominent non-motor features consistent with LBD, especially carriers of whole gene multiplications.[24,25] Besides these rare inherited cases, common non-coding variation at the *SNCA* locus has also been implicated in this form of dementia using GWAS approaches.[22,26] Pleomorphic risk genes, such as *SNCA*, are those in which rare, highly-penetrant mutations and common susceptibility variants contribute to the risk of a disease. The pleomorphic characteristics of *SNCA*, along with the fact that it encodes the protein that is the major component of Lewy bodies, underscore its pivotal role in the pathogenesis of LBD.[27]

The comparison of the *SNCA* risk variants in Parkinson's disease with those associated with LBD revealed notable differences at this locus.[22,28,29] In Parkinson's disease, the strongest association variant is within intron 4 of *SNCA*. In LBD, however, the primary signal is located closer to the 5'-region[29] and in close proximity to the non-coding antisense RNA *SNCA-AS1*, which modulates the *SNCA* expression in neurons. Integrative genomic evaluations examining the effect of the association variants on local gene expression nominated *SNCA-AS1* as the gene underlying disease risk in LBD.[22] The observed inverse relationship between *SNCA-AS1* and *SNCA* expression uncovers new therapeutic opportunities by suggesting that even a modest lowering of *SNCA* expression could be protective. Notably, the same signal has also been associated with REM sleep behavior disorder, a common prodromal manifestation of LBD.[30] However, the notion that increased expression of α-synuclein is driving disease has been recently called into question. Instead, synucleinopenia resulting from the sequestration of α-synuclein in Lewy bodies has been proposed as an alternative explanation.[31]

Another seminal discovery is the association of heterozygous variants within the gene encoding the lysosomal enzyme glucocerebrosidase (*GBA1*) with an increased risk of developing Parkinson's disease.[32,33] Homozygous or compound heterozygous mutations in *GBA1* cause Gaucher's disease, a lysosomal storage disorder with heterogeneous clinical features, including hepatosplenomegaly, bone disease, anemia, and neurological symptoms. The observation of a higher-than-expected risk of Parkinson's disease among family members of Gaucher's disease patients prompted further exploration of *GBA1*.[32,33] Parkinsonism due to *GBA1* mutations is commonly complicated by REM sleep behavior disorder and cognitive impairment, and subsequent association studies demonstrated a prominent role of *GBA1* variants in LBD.[22,26,28,30,34]

Research into genotype-phenotype correlations in *GBA1*-related neurodegeneration has provided further insights. Parkinson's disease patients carrying highly penetrant (severe) *GBA1* mutations, as defined by a standard classification scheme for Gaucher's disease,[35] have a higher risk of dementia progression than those with variants of lower effect size.[36] Furthermore, those with severe mutations can have a disease onset approximately five years earlier than mild mutation carriers.[37] Additionally, patients carrying *GBA1* mutations often have shorter life expectancy and are more likely to present with severe motor symptoms than non-carriers.[36]

The frequency, distribution, and effect sizes of *GBA1* risk alleles vary across populations. In LBD patients of European descent, about 13% of cases carry risk variants,[34,38] rising

to about 31% among Ashkenazi Jewish populations.[39] Detecting variants in the *GBA1* locus is challenging due to a nearby pseudogene with high sequence homology. The mechanism by which mutations in *GBA1* lead to neurodegeneration is still a topic of ongoing debate. A reciprocal relationship between glucocerebrosidase activity and α-synuclein expression exists, with decreased activity leading to increased α-synuclein aggregation.[40] These data favor the hypothesis that haploinsufficiency is the predominant molecular mechanism in *GBA1*-related neurodegeneration, and this observation might prove critical for developing targeted therapies.

Homozygous or compound heterozygous pathogenic mutations in *VPS13C*, which encodes vacuolar protein sorting 13 homolog C, are a rare cause of an autosomal recessive form of Lewy body disease.[41] The clinical presentations are heterogeneous and include early-onset parkinsonism with rapid progression and cognitive decline.[41-43] On a molecular level, mutations in this gene lead to mitochondrial dysfunction and mislocalization of *VPS13C* in the cytoplasm.[41,43]

Although many LBD risk genes overlap with those associated also with other neurodegenerative diseases, notable differences are also evident. For instance, the genes *MAPT* and *LRRK2* have been reproducibly associated with the risk of developing Parkinson's disease within cohorts of European ancestry.[44-46] However, despite sufficiently powered studies, no associations between these genes and susceptibility to LBD have been identified.[22,26,47] These findings suggest that the genetic architecture of LBD only partially intersects with Parkinson's disease.

Insights from Alzheimer's Disease Genetics

Genetic studies have established a connection between the *APOE* gene, encoding apolipoprotein E, and the risk of Alzheimer's disease. Individuals with the *APOEε4* allele have a threefold increased risk of developing Alzheimer's disease compared to the general population, while homozygous carriers have a 15-fold increased risk.[48] Numerous candidate gene studies have shown that *APOEε4* is similarly linked to higher risk for LBD, with the same dose-dependent associations as found in Alzheimer's disease.[34,49] Further, like Alzheimer's disease, the *APOEε2* allele decreases the risk for LBD.[50,51] Recent evidence has shown that *APOEε4* is a significant modifier gene that increases the risk of progression from Parkinson's disease to PDD.[52]

However, it remains unclear whether *APOEε4* impacts the risk for α-synuclein pathology independently of amyloid-β deposition. The *APOEε4* allele directly regulates α-synuclein deposition in transgenic mouse models that overexpress human *APOE* isoforms.[53,54] However, in neuropathologically confirmed human series, an association with *APOEε4* is only observed when Alzheimer's disease copathology is present.[49,55] This observation suggests that *APOEε4* might influence α-synuclein pathology in the presence of Alzheimer's disease, but more research is needed to fully understand this relationship. Several inherited forms of Alzheimer's disease can have prominent Lewy body co-pathology and mixed clinical presentations of both LBD and Alzheimer's disease. However, pathogenic mutations in *PSEN1* (encoding presenilin 1), *PSEN2* (encoding

presenilin 2), and *APP* (encoding amyloid β precursor protein) can rarely be found in LBD cases.[34,56,57] These findings emphasize the close molecular genetic relationship between LBD and Alzheimer's disease.

Other Genes Implicated in LBD

Progranulin is a ubiquitously expressed growth factor involved in processes relevant to neurological disorders, such as neural circuit development, lysosomal homeostasis, and neuroinflammation.[58,59] Researchers identified loss-of-function mutations in the *GRN* gene encoding this protein as a common cause of frontotemporal dementia.[60] More recently, the gene has been implicated in other neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease,[45,61,62] indicating that this locus has pleiotropic effects. Lewy body co-pathology has also been identified in the brains of FTD patients carrying *GRN* mutations.[62,63]

Subsequent genetic studies identified pathogenic loss-of-function mutations in *GRN* as a rare cause of autosomal dominant dementia with prominent Lewy body and TDP-43 co-pathology and clinical features resembling LBD.[64] *GRN* mutations accounted for less than one percent of cases of LBD in a European ancestry cohort.[64] Despite being rare, finding a *GRN* mutation in a patient could have clinical significance, as there are ongoing clinical trials for targeted treatments of this genetic form of neurodegeneration.[65]

Insights from Genome-wide Analyses

The application of modern genomic approaches has revealed additional crucial insights into the complex genetic architecture of LBD. In prior candidate gene studies, common genetic variants in the *SNCA*, *GBA1*, and *APOE* loci have been associated with LBD. Later on, GWAS approaches confirmed these associations.[22,26,47]

Additional association signals were discovered on chromosome 4 within the gene *TMEM175* (encoding transmembrane protein 175), an endolysosomal gene previously linked to Parkinson's disease, and on chromosome 2 near *BIN1* (encoding bridging integrator 1), a locus implicated in Alzheimer's disease.[22] Using a GWAS of structural variants, Kaivola and colleagues discovered an association between a 300-base pair deletion in the gene *TPCN1* and LBD.[66] This locus had an odds ratio of 1.4 and was found in 8% of LBD cases, highlighting its vital role in the pathogenesis. *TPCN1* encodes two pore segment channel 1, a voltage-dependent calcium channel located at the endolysosomal membranes.[67] Interestingly, this gene has also been suggested as a risk locus for Alzheimer's disease.[68]

Taken together, these observations illustrate the intricate connections between LBD, Alzheimer's disease, and Parkinson's disease. Polygenic risk assessments in LBD case-control cohorts have provided further insights and showed that LBD patients have an increased risk for both neurodegenerative diseases, even after accounting for the *APOE* and *GBA1* high-risk loci.[22,69] These findings suggest polygenic contributions play a role in determining an individual's susceptibility to LBD. They also show that Alzheimer's disease, Parkinson's disease, and LBD are considered part of a disease continuum.

Under this paradigm, LBD has clinical, pathological, and molecular features of both Alzheimer's disease and Parkinson's disease.

Pathway analysis based on the combination of genetic variables helps us gain a deeper understanding of the biological processes underlying LBD.[69] Several cellular mechanisms involved in LBD are related to pathways affected in Alzheimer's disease or Parkinson's disease. These pathways include the regulation of amyloid-β formation, regulation of endocytosis, tau protein binding, and lysosomal dysfunction.[22]

Recent evidence also shows a genetic overlap between Dementia with Lewy Bodies and cardiovascular diseases (hypertension, diabetes mellitus, hyperlipidemia).[70] These relationships hold therapeutic significance, as many cardiovascular risk factors can be modified. Other studies have suggested connections between LBD and the adaptive immune system, and with neuropsychiatric conditions, notably schizophrenia.[71,72]

4. NEUROPATHOLOGY OF LEWY BODY DEMENTIA

Lewy pathology results from the aggregation of α-synuclein in intraneuronal cytoplasmic inclusions that are pathognomonic for LBD (and Parkinson's disease). Lewy pathology occurs in axons and, to a lesser extent, in dendrites—both referred to as Lewy neurites—as well as in neuronal soma, known as Lewy bodies (Figure 2). Lewy bodies are highly variable in shape, and it is thought that they can disrupt key cellular functions, ultimately leading to neurodegeneration. Lewy neurites are thought to form first and move centrally to the neuronal soma, creating morphologically diverse aggregates that later condense into mature fibrillar Lewy bodies.[73-75] Recent modeling has shown that mature Lewy bodies take just under a decade to reach their maximum size, regulated by the production rates of both lipid membrane fragments and α-synuclein monomers from a malfunctioning degradation machinery.[76] Thus, Lewy pathology causes progressive neuronal dysfunction for a considerable time prior to neuronal degeneration due to disruption of cellular functions.[77]

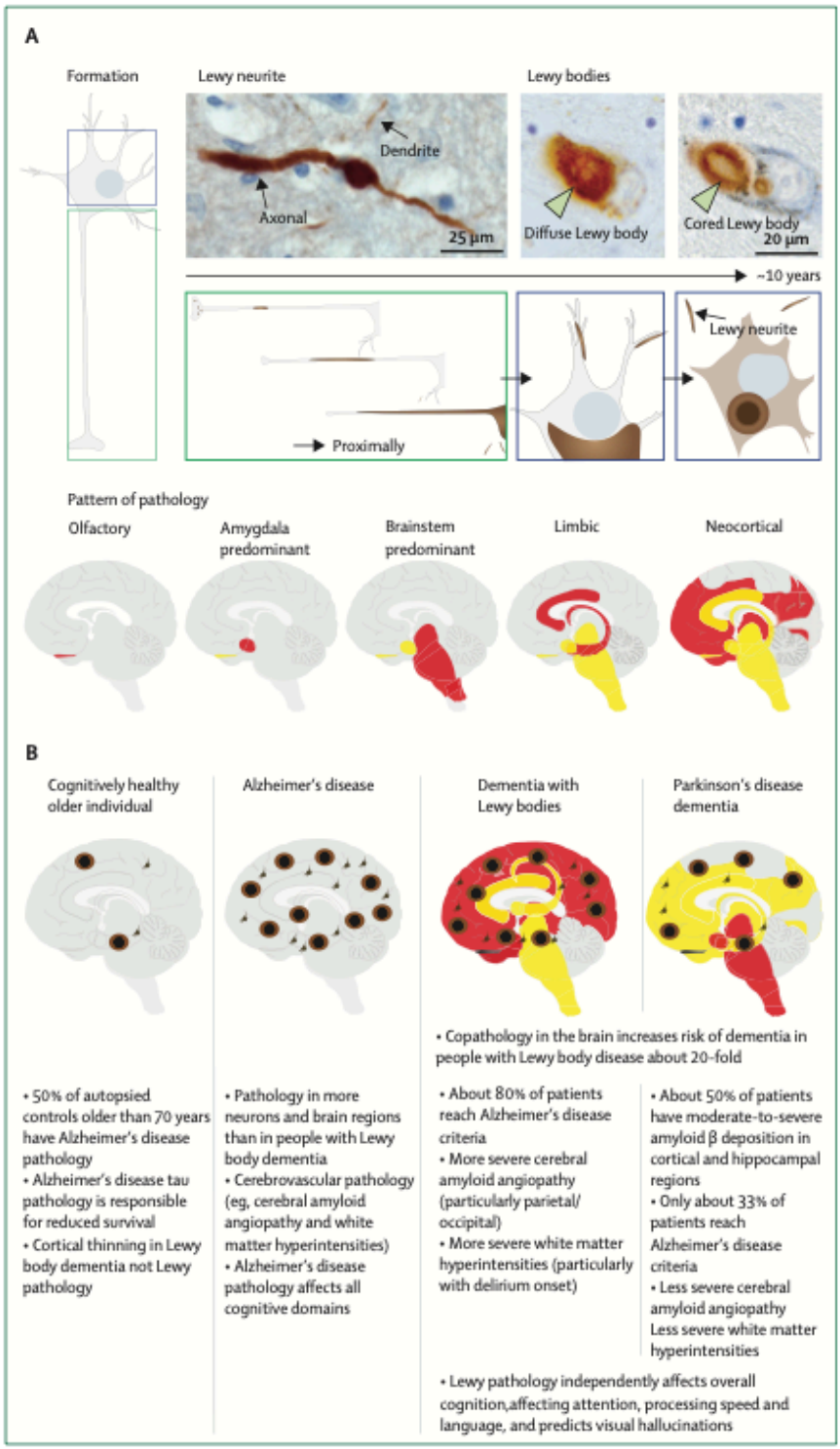

Figure 2: **The neuropathology of Lewy body dementia**
(A) The scheme of a typical neuron (left) indicates the areas of formation of Lewy pathology; α-synuclein first accumulates in Lewy neurites in the axons and dendrites, and then centrally in the neuronal soma, forming Lewy bodies. Five patterns of Lewy pathology can be distinguished: olfactory, amygdala-predominant, brainstem-predominant, limbic, and neocortical pattern. Red colour indicates brain regions with predominant Lewy pathology for a given pattern. Yellow colour indicates regions where Lewy pathology can be either present or absent. (B) Common copathologies in typical ageing, Alzheimer's disease, dementia with Lewy bodies, and Parkinson's disease dementia. Brown and black ovals indicate Alzheimer's disease pathology.

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The presence of Lewy pathology in the brain does not mean that a clinical LBD syndrome is inevitable; rather, it is the regional distribution of the pathology that is important. An autopsy study involving an elderly cohort found that 24% of cognitively normal individuals had Lewy body pathology.[78] However, Lewy pathology in the neocortex, which is the most common, or in limbic brain regions, is associated with a three- to five-times higher risk of dementia compared to Lewy pathology found elsewhere.[79-81] In the neocortex, only specific neurons are impacted by Lewy pathology—namely, layer 5 and 6b neurons[82] — which are integral to enhancing attention and neural activity.[83] Although Lewy pathologies in these critical cortical neurons are prevalent in most patients with LBD, those with a dementia dominant syndrome can have Lewy pathology confined to the amygdala,[79,84] affecting neurons involved in cognition, motivation, and stress responses. The amygdala is often involved in degenerative dementias and is considered an 'incubator' for misfolded proteins,[85] with specific truncated forms of highly aggregating α-synuclein that are unique to this region in LBD.[84]

Diagnostic Criteria for Lewy Body Disease Pathology

The neuropathological consensus criteria for Lewy pathology are based on determining the distribution of Lewy pathology in the brain.[79] Incorporating regional differences is due to the recognition that Lewy pathology is often not widespread but occurs in different patterns in selective neurons in predilection regions of the brain. These patterns match imperfectly to clinical syndromes, and so the consensus is to describe the pattern in any individual and diagnose one of five regional patterns assessed by the presence or absence of the pathology (Figure 2).[79] The five regional patterns of Lewy pathology are: 1) olfactory only, 2) amygdala predominant, 3) brainstem, 4) limbic, and 5) neocortical.

Part of the reason these patterns of Lewy pathology imperfectly match clinical syndromes is the coexistence of Alzheimer pathology in LBD. For this reason, the neuropathological diagnostic criteria for Dementia with Lewy Bodies takes Alzheimer copathology into consideration, requiring the assessment of this copathology for definitive diagnosis.[1] A Dementia with Lewy Bodies diagnosis is assigned only to those that do not meet the criteria for intermediate or severe amounts of Alzheimer's disease neuropathologic change, as in those cases the dementia syndrome is unlikely to be due to the Lewy pathology.[1] Approximately 65% of all dementia cases meet Alzheimer's disease neuropathological criteria.[86,87]

It should be noted that 1) Alzheimer pathology affects a considerably greater volume of brain tissue than Lewy pathology, depositing extracellular as well as intracellular proteins in more neurons in more brain regions; 2) Alzheimer pathology is highly prevalent with aging (at least 50% of all autopsied cases having some degree of hippocampal and cortical Alzheimer pathology by the age of 70,[88] including those but with Lewy pathology);[89] 3) even a low degree of copathology in the brain (Alzheimer or Lewy pathology) increases the risk of transitioning to dementia 20-fold;[87,89] and 4) Alzheimer tau pathology is responsible for reduced survival and cortical thinning in people with LBD not Lewy pathology.[90,91]

Regarding the prevalence of copathologies in LBD, it differs depending on whether the patient has a dementia presentation, such as Dementia with Lewy Bodies, or a motor presentation that progresses to dementia after at least one year from motor symptom onset (Parkinson's Disease Dementia). Nearly 80% of Dementia with Lewy Bodies cases have intermediate to severe Alzheimer's copathology,[92,93] while 50% of Parkinson's Disease Dementia cases have moderate to severe amyloid-β deposition in cortical and hippocampal regions (but not in other brain regions), while only a third have additional tau pathology that meets diagnostic criteria for Alzheimer neuropathologic change.[80,92,93] In Parkinson's Disease Dementia, the reduced accumulation of amyloid-β is reflected by less compact and less structured tau, indicating a later occurrence in Alzheimer copathology in Parkinson's Disease Dementia compared to Dementia with Lewy Bodies.[94] It is important to note that in Parkinson's disease, amyloid-β copathology is associated with a more rapid cognitive decline and mortality than in cases with pure Lewy body pathology.[80,95,96]

The differences in Alzheimer's copathology prevalence between Dementia with Lewy Bodies and Parkinson's Disease Dementia are also reflected in the prevalence, distribution, and severity of other Alzheimer's disease-associated pathologies, i.e., cerebral amyloid angiopathy[89,97-99] and TDP-43 pathology.[80,89] Of note, in Parkinson's Disease Dementia, cerebrovascular and TDP-43 pathologies are not correlated with dementia,[80] supporting the concept that these copathologies are not driven by Lewy pathology.

A considerable effort has gone into assessing the relative contributions of mixed pathologies to cognition. The latest data from the Alzheimer's Coordinating Centers in the United States indicate that the total number of copathologies per individual directly correlates with cognitive performance, except for cerebrovascular and uncommon pathologies which have more variable effects[87,100] Lewy pathology has an independent effect on overall cognition, influencing attention, processing speed, and language, whereas Alzheimer's pathology affects all cognitive domains.[100] Additionally, Lewy pathology is associated with visual hallucinations, that can occur in patients with LBD.[87]

5. MOLECULAR PATHOGENESIS OF LEWY BODY DEMENTIA

Mitochondrial and lysosomal dysfunction,[101-103] neuroinflammation,[71,104,105] as well as synaptic dysregulation and density loss are key pathways of LBD pathogenesis.[106,107] Mitochondrial dysfunction results in impaired energy production and increased oxidative stress, while lysosomal dysfunction results in aberrant degradation of α-synuclein, leading to increased synuclein accumulation and cellular toxicity. Neuroinflammation involves reactivity responses induced in microglia and astrocytes, contributing to neuronal damage. Synaptic dysregulation affects neurotransmitter release and synaptic plasticity, worsening cognitive decline (Figure 3).

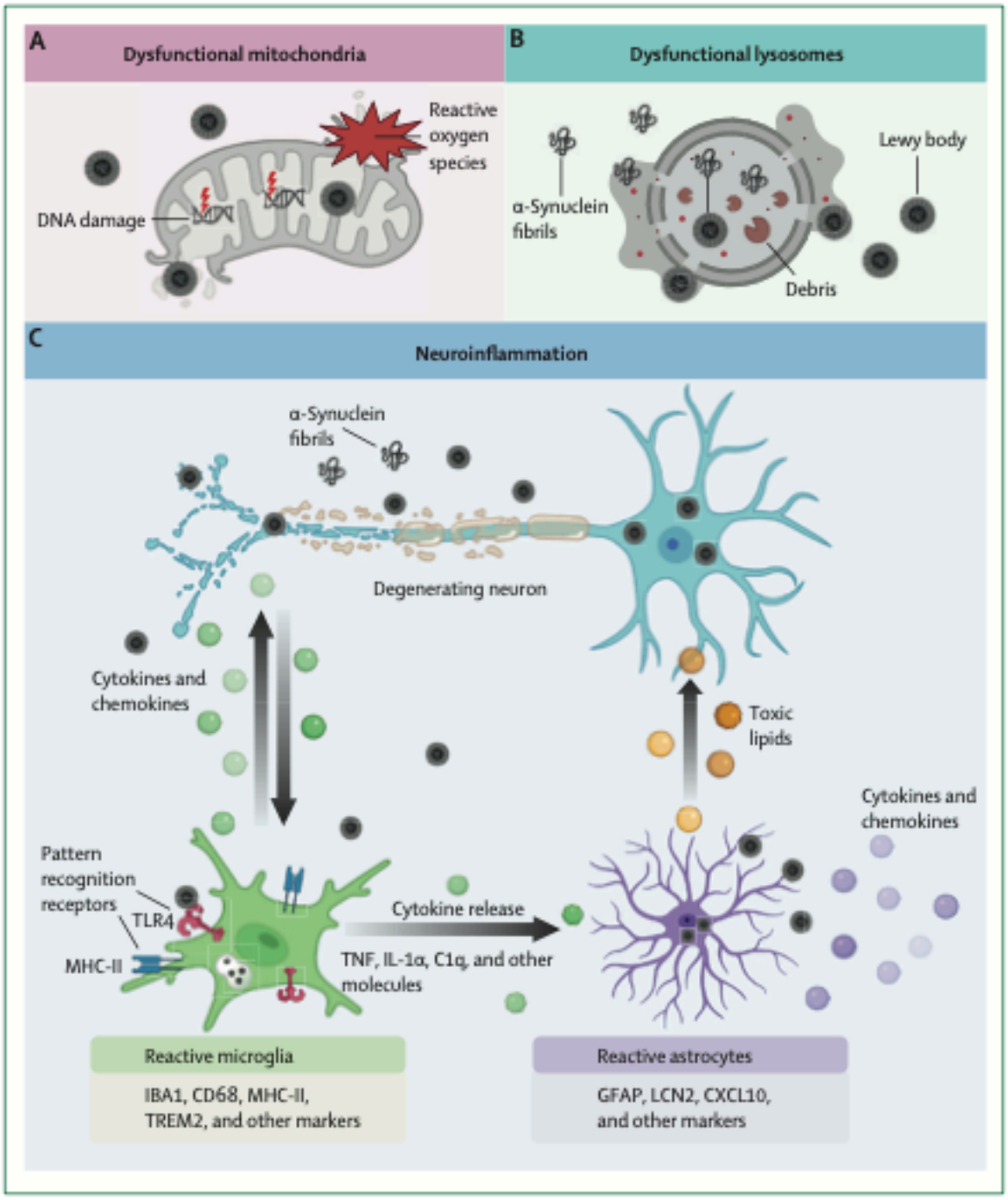

***Figure 3*: Molecular mechanisms in Lewy body dementia**

(A) Mitochondrial dysfunction leads to DNA damage and the production of reactive oxygen species, activating stress-related pathways. (B) Lysosomal dysfunction impairs protein clearance, resulting in the accumulation of Lewy bodies and contributing to cellular dysfunction and damage. (C) Microglial reactivity and phagocytic activity are induced by α-synuclein aggregates. This activation occurs through the engagement of pattern recognition receptors. Reactive astrocytes can also contribute to inflammation and neuronal death by secreting neurotoxic lipids, primarily very long-chain saturated free fatty acids.[122] These neurotoxic reactive astrocytes are generated in response to reactive microglia, which release inflammatory cytokines.[111] Figure created in BioRender.com.

Converging evidence underscores additional dysfunctions of protein degradation pathways, including impairments of the ubiquitin-proteasome system and dysregulation of the autophagy-lysosome pathway.[108] Other crucial dysfunctions include the posttranslational modification of α-synuclein and the formation of α-synuclein oligomers and prefibrillar structures that alter lysosomal trafficking and mitochondrial function;[109] differential expression of genes involved in astrocyte function and their alternative splicing isoforms are also pathological mechanisms;[110] B-cell involvement and T-cell lymphocytes, which are often reactive against α-synuclein.[111-113] However, the order in which these processes occur, the extent to which they are drivers of disease versus compensatory mechanisms, and how they interact is largely unknown. Understanding these molecular pathways is key to developing targeted therapies for LBD.

Emerging technologies, including single-cell/nucleus omics and spatial transcriptomics, can offer valuable insights into the mechanisms underlying LBD using postmortem brain tissue. Single-nucleus RNA sequencing will enable the identification of neuronal and glial cell subtypes specific to LBD. Spatial transcriptomics can further enhance this approach by mapping these unique cell types within vulnerable brain regions, facilitating a deeper understanding of region-specific pathological processes.

Mitochondrial and lysosomal dysfunction

LBD-associated genes influence mitochondrial and lysosomal functions through various mechanisms, including the regulation of mitophagy, oxidative stress response, and lysosomal protein clearance. For instance, misfolded α-synuclein aggregates resulting from pathogenic *SNCA* mutations can increase mitochondrial reactive oxygen species (ROS) production,[114,115] leading to neuronal toxicity and cell death.[114] Studies indicate that α-synuclein aggregates directly interact with cardiolipins—phospholipids specific to the mitochondrial membrane—disrupting membrane integrity and function. Additionally, misfolded α-synuclein can inhibit complex I of the electron transport chain, further elevating ROS levels.[116,117] Lewy body pathology has been detected in older individuals with mitochondrial disease caused by mutations in mitochondrial DNA or nuclear-encoded mitochondrial genes,[118] reinforcing the connection between mitochondrial dysfunction and Lewy body accumulation.

Lysosomal dysfunction is another key contributor to the impaired clearance of misfolded α-synuclein, leading to the buildup of Lewy body aggregates and disruption of cellular homeostasis. Genetic variants in *GBA1* and *TMEM175* are directly linked to defects in lysosomal degradation pathways.[22,58,103] Loss-of-function mutations in *GBA1* reduce glucocerebrosidase enzyme activity, causing glucocerebroside to accumulate within lysosomes.[119] This lipid buildup alters lysosomal pH, impairs hydrolase activity, and affects α-synuclein metabolism.[103] Similarly, *TMEM175* variants that impair lysosomal potassium channel function disrupt pH homeostasis, reduce protease activity, and impair autophagic flux, further preventing protein degradation and promoting α-synuclein aggregation.[120] These lysosomal deficits drive the formation of Lewy body inclusions in neurons. Importantly, genetic variants affecting lysosomal function, such as variants in *GBA1*, are associated with faster cognitive decline and more severe Lewy pathology.[121]

Immune System Involvement and Inflammatory Mechanisms

Inflammation is a crucial component of pathophysiology of many diseases including LBD. In the central nervous system (CNS), inflammation is driven by reactive glia, including microglia and astrocytes. Glia modulate cell-intrinsic and extrinsic pathways of neuronal cell death (Figure 3).[122,123]

Neuroinflammation is primarily driven by microglia, the brain's resident macrophages.[124] In healthy tissue, microglia display a ramified morphology and actively clear misfolded protein aggregates and cell debris through phagocytosis.[124] However, in response to pathological insults, such as α-synuclein-rich dystrophic neurites or extracellular α-synuclein aggregates from spilled-over Lewy body components, resting microglia can become "reactive" and adopt a more spheroidal, amoeboid morphology with altered functions. α-Synuclein aggregates induce microglial reactivity and phagocytic activity in both *in vitro* (cell culture) and *in vivo* (rodent) models.[125-127]

The distribution of the reactive microglia provides important insights. Ionized calcium-binding adaptor molecule 1-positive ($IBA1^+$) microglia with spheroidal, beaded, de-ramified, or fragmented processes have been identified in the CA1 region of the hippocampus of LBD patient brains.[128] Several of these microglia were positive for CD68, a lysosomal marker associated with phagocytic activity, suggesting active clearance of extracellular α-synuclein aggregates and/or Lewy body-laden neurites by microglia.[128,129]

However, the concept that reactive microglia directly cause neuronal toxicity has been questioned. Instead, chronically active microglia can adopt “disease-associated” phenotypes characterized by dysfunctional states, such as impaired phagocytosis or ineffective clearance of toxic debris. In one study, microglia containing α-synuclein aggregates were shown to transfer these aggregates to healthy microglia through tunneling nanotubes to facilitate their clearance.[130] Interestingly, the donor microglia that offloaded the aggregates also received healthy mitochondria from the recipient microglia. Together, these findings suggest that in LBD, microglia engage in dynamic interactions with other microglia and injured neurons to exchange α-synuclein and support tissue repair. Rather than contributing to neurotoxicity, these studies highlight a potentially neuroprotective role for reactive microglia.

Astrocytes are the most abundant type of glial cell in the CNS and support neurons via the secretion of neurotrophic and metabolic factors, regulation of ion homeostasis, and maintenance of synaptic activity.[131] Like microglia, astrocytes also become reactive in neurodegenerative diseases and have altered morphology and function (Figure 3).[132-134] Astrocytes with increased immunoreactivity for glial fibrillary acidic protein ($GFAP^+$), a historical but poor marker of reactive astrocytes, have been found in close proximity to extracellular α-synuclein-positive Lewy bodies in brains from patients with.[135] Astrocytes with α-synuclein aggregates have been detected in several regions of the LBD patient brains, including the hippocampus, substantia nigra, amygdala, and cortex.[136,137] However, how and why α-synuclein accumulates in astrocytes and the consequences of astrocytic α-synucleinopathy remain unclear.[136]

The interplay between microglia and astrocytes is central to the inflammatory processes occurring in LBD (Figure 3). Glial cells are highly heterogeneous, with different substates of microglia and astrocytes having varied functions in response to pathological conditions and environmental stimuli.[138] Advances in transcriptomics, proteomics, and metabolomics have revealed new subpopulations of glial cells in various pathological contexts, which are being validated in both human beings and rodent models.[139,140] Continued mining of such datasets will likely identify additional functional interactions between microglia and astrocytes that are perturbed in LBD – findings that are crucial for pinpointing specific cell types and novel drug targets.

The involvement of microglia and astrocytes (as well as other non-neuronal cells in the CNS, such as oligodendrocyte lineage cells and endothelial cells) may vary considerably across different genetic forms of LBD, parkinsonism, and other dementias.[141-145] The specific genetic mutation often determines the primary glial cell type involved and the regional distribution of glial reactivity. Mutations in *SNCA* are linked to increased α-synuclein expression and aggregation, which coincides with reactivity in both microglia and astrocytes.[136,146,147] In Alzheimer's disease, frontotemporal dementia, and LBD, glial responses involving microglia and astrocytes are closely associated with the primary accumulating protein (e.g., amyloid β, tau, TDP-43, α-synuclein) and the resulting neuropathology.[148] Therefore, the relative contribution and characteristics of microglial versus astrocyte pathology are a direct consequence of the underlying genetic defect and the resulting disease mechanisms.[145]

5. CONCLUSIONS AND FUTURE DIRECTIONS

Advances in the genetic and pathological characterization of LBD have dramatically accelerated our understanding of this neurodegenerative condition. The genetic architecture of LBD is complex, with both common and rare variants contributing to disease susceptibility. While a significant portion of the heritability of LBD remains elusive, substantial knowledge has been acquired through the examination of related neurodegenerative disorders, illustrating that the LBD risk profile partially overlaps with those of Parkinson's disease and Alzheimer's disease. Although these insights are not comprehensive, they provide crucial perspectives on pathophysiological mechanisms, highlighting the impairment of lysosomal function, dysfunction of mitochondrial homeostasis, and neuroinflammation as critical factors. Nevertheless, significant knowledge gaps persist (Panel 2). Increased efforts to study clinically and pathologically well-characterized cohorts across the natural history of LBD are essential. Incorporating multi-omic data within a systems biology framework will enhance insights into the dynamic networks of interacting components at the cellular and tissue levels. As our molecular understanding expands, there is increasing optimism that this knowledge will improve disease modeling and ultimately facilitate its translation into therapeutic targets.

Contributors

All authors contributed to the conceptualization of this review. SWS coordinated the writing of this manuscript. All authors contributed equally to the literature search, design of display items, and writing.

Declaration of interests

SWS serves on the Scientific Advisory Council of the Lewy Body Dementia Association, Mission MSA, and the G-Can initiative. SWS receives research support from Cerevel Therapeutics. SWS is an editorial board member for JAMA Neurology and the Journal of Parkinson's Disease. SAL maintains stock options as a financial interest in AstronauTx Ltd. and Synapticure. SAL is an editorial board member for Glia and Cell Reports and serves on the Scientific Advisory Board of RM Global, Catalyst for a Cure (Glaucoma Research Foundation), Concept Life Sciences, and the Tambourine ALS Research Program. MR serves on the Scientific Advisory Board of Astex. GMH is an editorial board member of Acta Neuropathologica, Journal of Parkinson's Disease, Neurobiology of Disease, Neuropathology and Applied Neurobiology, Science Advances, and Translational Neurodegeneration. All other authors report no competing interests.

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Search strategy and selection criteria

References for this Review were identified by searches of PubMed between 2015 and May 2025, by use of the following terms: "Lewy body," or "Lewy body dementia" or "Parkinson disease dementia" or "dementia with Lewy bodies" in combination with "pathology," "genetics," "biomarker," "RT-QuIC," "alpha-synuclein," "synucleinopathy," or "molecular." Bibliographies of papers were also reviewed. Papers published in English were considered. The final reference list was generated based on relevance to the topics covered in this Review.

PANELS

Panel 1: **Influence of Sex on LBD**

The data regarding the sex distribution of LBD are conflicting.[149,150] Of the eight studies that reported sex data, half found a higher male incidence, and the converse for the other half. The small cohorts reported in these studies and the predominance of prevalence-derived estimates mean that caution is required in interpreting the findings.

In contrast, neuropathological studies indicate a consistent over-representation of males in cases of Lewy body pathology consistent with LBD. Males have more frontal atrophy on neuroimaging than women.[151] Sex differences might decline with age, especially above age 75. The severity of dementia in Dementia with Lewy Bodies is reportedly higher in females, presumably due to a higher burden of Alzheimer's disease co-pathology.[152] In contrast, the effect of sex on disease progression and survival is similar in men and women.[152]

Longitudinal data indicate that the probability of dementia in Parkinson's disease varies by disease duration and is 27% at ten years of disease, 50% at 15 years, and 74% at 20 years.[153] Male sex is a risk factor for the development of cognitive decline in Parkinson's disease.[154] Considerable heterogeneity has been observed in the cognitive profile of patients with Parkinson's disease, which has been attributed to the effect of individual risk factors (such as genetics) modulating the underlying brain pathology, and the presence of Alzheimer's disease co-pathology.[155-157]

Panel 2: Research priorities for the genetic and pathological characterization of LBD

Defining the genetic architecture of LBD

- Increase the cohort size of patients with longitudinal clinical, molecular, and pathological information across the natural history of LBD to improve the power of gene discovery efforts (i.e., investigating the missing heritability).
- Enhance recruitment of ancestrally diverse individuals.
- Increase recruitment of familial LBD cases.
- Improve investigations into less studied genetic variants and their role in LBD (e.g., copy number variants, somatic mutations, repeat expansions).

Integrating multi-omic data

- Integrate epigenomic, genomic, transcriptomic, proteomic, metabolomic, and environmental data to interpret molecular discoveries within a systems biology framework.
- Expand innovative data analysis techniques.
- Create foundational molecular resources to accelerate drug discovery and repurposing.
- Expand data sharing to ensure reproducible research practices.

Understanding the contributions of Lewy body pathology and co-pathologies

- Increase the number of autopsies in deeply characterized LBD cases.
- Develop scalable methods to assess LBD-associated pathologies.
- Improve the harmonization of pathological data and enhance best practices for neuropathological evaluations.
- Expand deep learning techniques and automated digital image analysis.
- Investigate the relationship between novel biomarkers and LBD pathology.

Investigating the mechanisms associated with the onset and progression of LBD

- Increase insights into cellular pathogenesis using single-cell models, assembloids, and spatial transcriptomic approaches.
- Expand the availability of *in vitro* and *in vivo* models using genetic engineering approaches.
- Investigate posttranslational modifications and the conformational state of α-synuclein in modulating protein aggregation, seeding capacity, and toxicity.
- Investigate the molecular underpinnings of the clinical and pathological heterogeneity of LBD.
- Develop and improve biomarkers of key biological processes.
- Translate genetic variants into disease mechanisms and therapeutic targets.

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