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Exploring the link between GBA1 mutations and Dementia with Lewy bodies, A mini-review

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ABSTRACT

Importance: Dementia with Lewy bodies (DLB) is a neurodegenerative disease linked to abnormal accumulation of phosphorylated α-synuclein. GBA1 is the gene encoding the lysosomal enzyme glucocerebrosidase (GCase), whose mutations are a risk factor of DLB.
Objective: To report all available data exploring the association between GBA1 mutations and DLB.
Evidence Review: All publications focused on GCase and DLB in humans between 2003 and 2022 were identified on PubMed, Cochrane and ClinicalTrials.gov.
Findings: 29 studies were included and confirmed the strong association between GBA1 mutations and DLB (Odds Ratio [OR]: 8.28). GBA1 mutation carriers presented a more malignant phenotype, with earlier symptom onset, more severe motor and cognitive dysfunctions, more visual hallucinations and rapid eye movement sleep disorder. GBA1 mutations were associated with "purer" neuropathological DLB. No therapeutic recommendations exist and clinical trials targeting GCase are just starting in DLB patients.
Conclusions and Relevance: This review reports a link between GBA1 mutations and the DLB phenotype with limited evidence due to the small number of studies.

1. Introduction

Dementia with Lewy Bodies (DLB) is the second most common cause of neurodegenerative dementia, accounting for 10–15 % of all cases (McKeith, 2004) and belongs to the group of Lewy body (LB) diseases including Parkinson's Disease, DLB and multi-system atrophy. LB are intraneuronal proteinaceous inclusions composed of abnormal aggregates of phosphorylated α-synuclein (SNCA) in the nervous system (McKeith et al., 2017). According to the criteria, DLB patients suffer from neuropsychiatric symptoms, motor symptoms of parkinsonism as well as fluctuations, excessive daytime somnolence and sleep disorders.

The lysosomal enzyme glucocerebrosidase (GCase) is responsible for the breakdown of glucocerebroside into glucose and ceramide. Homozygous mutations in the GCase gene GBA1 cause GCase deficiency leading to glucocerebroside accumulation inside the lysosome. This accumulation results in Gaucher disease, the most frequent lysosomal storage disorder (Stirnemann et al., 2017). Since several patients with Gaucher disease present with parkinsonism and have GBA1 mutation-carrier relatives with Parkinson's disease (PD), subsequent studies have revealed that GBA1 mutations are associated with PD and

List of abbreviations: DLB, dementia with Lewy bodies; GCase, glucocerebrosidase; LB, Lewy body; SNCA, α-synuclein; PD, Parkinson's disease.

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with DLB (Li et al., 2015; Goker-Alpan et al., 2006; Mata et al., 2008; Sidransky et al., 2009; Nalls et al., 2013). GBA1 mutations causing Gaucher disease have been categorized as "severe" (L444P, for example) or "mild" (N370S, for example) based on their contribution to the phenotype of GD among homozygotes (Beutler et al., 2005). It has also been shown that the severity of the PD phenotype is related to the severity of the mutation in the GBA1 gene (Thaler et al., 2018; Brockmann, 2020).

Most previous reviews have focused on characterizing GBA1-associated PD, but, to the best of our knowledge, no review has yet summarized clinical research evidence in GBA1-associated DLB, including epidemiology, neuropathology, fluid biomarkers as well as clinical characteristics. This review will highlight current clinical research linked to GBA1 mutations, GCase activity and DLB, that may yield new therapeutic strategies.

2. Methods

This systematic review was conducted according to PRISMA guidelines (Moher et al., 2009). All published articles between January 1, 2003, and April 1, 2022, were identified on PubMed and Cochrane using the Medical Subject Heading (MeSH) terms ("glucocerebrosidase" OR "GBA") AND ("Lewy body OR "Lewy bodies"). In addition, the ClinicalTrials.gov database was searched using the same search terms. Additional studies were included from the reference lists of relevant studies. Studies were included if they focused on GCase and DLB in humans. Titles and abstracts were the base of the initial screening. We evaluated the eligibility of selected articles after full text readings. Preclinical studies (cell lines or animal models) were excluded, as well as studies focusing only on PD; studies published in languages other than English, Reviews, Opinion papers and Duplicates were excluded. Data including study design, number of subjects, demographic data, clinical, genetic, biological, pathophysiological and neuropathological characteristics, main outcomes measures, main results and conclusions were extracted by 8 authors according to their field expertize (CP JH SG CH FM-L EA MF PM) using a standardized extraction form. The strength of clinical data were graded according to the Oxford Center for Evidence-Based Medicine (OCEBM) levels of evidence (Oxford Centre for Evidence-Based Medicine, 2009). The OCEBM framework levels range from 1 to 5, with 1 the highest level of evidence (Properly powered and conducted randomized clinical trial; systematic review with meta-analysis) and 5 the lowest level (expert opinion without explicit critical appraisal). Level 2 evidence is obtained from well-designed controlled trials without randomization or prospective comparative cohort trials. Level 3 corresponds to case-control studies or retrospective cohort studies, and level 4 refers to case-series. Studies that ranked level 5 on the OCEBM scale were excluded.

3. Results

232 studies were screened and assessed for eligibility. After applying inclusion and exclusion criteria (Supplementary Fig. 1), 29 clinical studies were selected for inclusion. We summarized clinical study findings and evidence levels in Table 1.

3.1. Clinical studies

3.1.1. Epidemiologic and cohort studies

Epidemiological studies have demonstrated that heterozygosity for common mutations in the GBA1 gene have been more frequent among patients with DLB than in the general population. As detailed in Table 1, the frequency of the most common mutations in GBA1 gene was highly variable, from 3 % to 31 % of DLB cases (Goker-Alpan et al., 2006; Mata et al., 2008; Clark et al., 2009; Shiner et al., 2016; Setó-Salvia et al., 2012; Nishioka et al., 2011; Farrer et al., 2009). Furthermore, the strong association between GBA1 mutations and DLB (OR: 8.28) was higher than reported in PD (OR: 5.43) and in PD with dementia (OR: 6.48) (Sidransky et al., 2009; Nalls et al., 2013). In addition to the two mutations most frequently associated with PD (N370S and L444P), the E326K variant is over-represented in DLB patients and is strongly associated with pure-DLB. In an Ashkenazi Jews cohorts of patients diagnosed with DLB, about 30 % are carriers of mutations in the GBA1 gene (Shiner et al., 2016, 2021). Concerning the sex ratio in GBA1-associated DLB, several studies have observed a higher rate of men (from 65 % to 90 %) in all mutation carriers (Gámez-Valero et al., 2016).

3.1.2. Human neuropathology

Neuropathological studies suggest a strong association between GBA1 mutation and LB-type pathological changes. GBA1 mutation status was significantly associated with the presence of cortical LBs and GBA1 mutation carriers were significantly less likely to meet AD neuropathological criteria. In a retrospective cohort study of 213 autopsy-confirmed LB spectrum disorders patients, Irwin et al., 2017 reveal a decreasing frequency of heterozygous patients carrying the GBA E326K risk allele or GBA1 mutation with increasing levels of AD neuropathology (Irwin et al., 2017). Thus, GBA1 mutations may be associated with pathologically "purer" LB disorders, characterized by a more diffuse pattern of LB distribution involving the cerebral cortex, and less severe AD pathological findings (Clark et al., 2009; Tsuang et al., 2012; Goker-Alpan et al., 2010). In parallel, a few studies have shown decreased GCase protein and mRNA levels and reduced GCase enzyme activity in the brains of DLB with or without GBA1 mutations compared to controls (Kurzawa-Akanbi et al., 2012; Perez-Roca et al., 2018; Moors et al., 2019). However, population stratification based on GBA1 genotype demonstrated substantially lower GCase activity in carriers than in non-carrier, both in the study by Moors et al. (2019) in DLB patients and in the study by Clark et al. (2015) in patients with LB spectrum disorders (Moors et al., 2019; Clark et al., 2015). In 2019, Gündner et al (Gündner et al., 2019) demonstrated that in the substantia nigra, reduced GCase levels contribute to the increase in SNCA levels and to DLB disease manifestation partly by increasing its glycolipid substrate glucosylsphingosine. This result was concordant with a more pronounced alteration of lipid profiles in LB disease brains of GBA1 mutation carriers compared to non-carriers (Clark et al., 2015). In 2021, Kurzawa-Akanbi et al (Kurzawa-Akanbi et al., 2021) showed that extracellular vesicles purified from LB disorders *post-mortem* CSF and frontal cortex were heavily loaded with ceramides and neurodegeneration-linked proteins including SNCA and tau. However, GBA1 carriers did not show greater sphingolipid levels than non-carriers. These findings indicate that abnormalities in ceramide metabolism are a feature of LB disorders, and that GBA1 modulates the risk of alpha-synucleinopathies, rather than induces it, and extracellular vesicles are likely involved in disease propagation.

3.2. Clinical characteristics

All clinical studies are summarized in Table 1. To date, 7 studies assessed the clinical characteristics of patients with DLB and GBA1 mutations between 2003 and 2022. All those studies have described that GBA1 mutation carriers were younger at symptom onset with more frequent hallucinations, more pronounced parkinsonism and poorer cognition (Nalls et al., 2013; Shiner et al., 2016, 2021; Gámez-Valero et al., 2016; Goker-Alpan et al., 2008; Bregman et al., 2019; Lerche et al., 2019).

3.2.1. Biological biomarkers

Concerning biological biomarkers, several approaches have used either CSF or peripheral blood to assess GCase, SNCA or GBA1 transcript variants in patients with or without GBA1 mutations. The corresponding 4 studies are described in Table 1 (Perez-Roca et al., 2018; Lerche et al., 2019; Parnetti et al., 2009). Unfortunately, all these studies have

Table 1
Summary of clinical studies. * Levels of evidence are as follows: level 1, properly powered and conducted randomized clinical trial; systematic review with meta-analysis; level 2, well-designed controlled trial without randomization; prospective comparative cohort trial; level 3, case-control studies and retrospective cohort studies; level 4, case series with or without intervention and cross-sectional study; level 5, opinion of respected authorities; case reports.

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Goker-Alpan, 2006 (Goker-Alpan et al., 2006)	Case-control	3	75	Epidemiology	Study role of GBA1 in autopsy-confirmed synucleinopathies	63 cases with LB pathological findings: 35 with cortical LBs (DLB or DLB-AD) and 28 with pure PD, and 12 MSA	All 11 exons and flanking intronic regions of GBA1 were sequenced	Mutations in the GBA1 gene in 4% of cases with PD, 23% of cortical LBs (8/35), and none in MSA
Mata, 2008 (Mata et al., 2008)	Case-control	3	1332	Epidemiology	Assess role of GBA1 variants in altering risk for LB disorders	721 patients with PD, 554 controls, and 57 patients with DLB	Presence or absence of the 2 most common GBA1 mutations (N370S and L444P)	Higher heterozygote frequency for the 2 GBA1 mutations in patients with PD (2.9%; P<.001) and DLB (2/57; 3.5%; P=.045) vs controls (2/554; 0.4%)
Nalls, 2013 (Nalls et al., 2013)	Case-control	3	2834	Epidemiology Clinical presentation and prognosis	Investigate GBA1 mutation carrier status as predicting DLB or PD with dementia	872 patients (721 DLB and 151 PD with dementia) and 1962 controls from 11 centers	• Frequency of GBA1 mutations • Demographics, age at onset, disease duration, clinical and pathological features	• Association between GBA1 mutation carrier status and DLB, OR: 8.28 (IC95%, 4.78–14.88) • Association between GBA1 mutation carrier status and PD with dementia, OR: 6.48 (IC95% 2.53–15.37) • Mean age at diagnosis of DLB earlier in GBA1 mutation carriers than in non-carriers (63.5 vs 68.9 years; P<.001), with higher disease severity scores
Clark, 2009 (Clark et al., 2009)	Case-control	3	187	Epidemiology Human neuropathology	Determine the relationship of GBA1 mutations and APOE4 genotype to LB and AD pathological findings	95 patients with primary neuropathological diagnoses of LB disorders with or without AD changes, 60 patients with AD (without significant LB pathological findings), 32 controls with neither LB nor AD pathological findings	• GBA1 mutation status (full genotyping of GBA1) • APOE4 genotype • LB pathological findings and Alzheimer plaque and tangle pathological findings	• GBA1 mutations in 18% of all subjects, including 28% (27 of 95) of subjects with primary LB compared with 10% (6 of 60) of subjects with AD and 3% (1 of 32) of subjects without AD or LB • GBA1 mutation status was significantly associated with the presence of cortical LBs (OR 6.48; IC95% 2.45–17.16; P<.001). GBA1 mutation carriers were significantly less likely to meet AD pathological diagnostic criteria (OR 0.35; IC95% 0.15–0.79; P=.01)
Shiner, 2016 (Shiner et al., 2016)	Case-control	3	35	Epidemiology Clinical presentation and prognosis	Evaluate clinical and genetic characteristics of an AJ cohort of DLB patients, assess association of DLB phenotype with GBA1 mutations, explore effects of mutations on disease clinical course	35 consecutively recruited AJ patients with newly diagnosed clinically probable or possible DLB	• Genotyping for the 7 known AJ GBA1 mutations and the LRRK2 G2019S mutation • Clinical markers: Autonomic Scale for Outcomes in Parkinson's Disease (SCOPA-AUT), RBD Single-Question Screen, GDS, MOCA • Motor scale (UPDRS III) • In 15 patients: Color Trail Making Test, FAS verbal fluency, Digit Span, Hooper Visual Organization Test, Stroop test	• 11/35 DLB patients (31%) carried GBA1 mutations • GBA1 mutation carriers were younger at symptom onset (mean [SD] age, 65.7 [11.7] vs 72.1 [5.1] years; P =0.03), had more frequent visual hallucinations (9 of 11 [82%] vs 12 of 22 [55%]; P = 0.052), and had higher RBD scores (mean [SD], 7.8 [2.2] vs 5.1 [3.3]; P = 0.03) • GBA1

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
								mutation carriers had poorer cognition as assessed by MOCA (mean [SD] score, 18.75 [5.99] vs 23.23 [3.16]; P = 0.03), lower scores on tests of verbal fluency (adjusted z scores, 0.50 vs −2.02; P = 0.02), worse scores on visuospatial tests (adjusted t scores, 68.55 vs 79.57; P =0.046), and higher mean (SD) scores on the UPDRS III (36.72 [10.62] vs 25.72 [10.32]; P = 0.03)
Seto-Salvia, 2012 (Setó-Salvia et al., 2012)	Case-control	3	428	Epidemiology	Study role of GBA1 mutations in clinical course of PD, including cognitive decline and dementia	225 PD patients, 17 pathologically confirmed LBD patients, and 186 controls from Spain	Full sequencing of GBA1 coding region	• 22 PD patients (9.8%) and 2 LBD patients (11.8%) carried mutations in the GBA1 gene, vs 1 control (0.5%). N370S and L444P mutations represented 50% of the alterations • Alterations in GCase were associated with a significant risk of dementia during the clinical course of PD (adjusted OR, 5.8; P =.001)
Nishioka, 2011 (Nishioka et al., 2011)	Case-control	3	59	Epidemiology Human neuropathology	Determine the frequency of GBA1 variants in clinically diagnosed and pathologically-confirmed cases of diffuse LBD	• 59 cases with pathological diagnosis of diffuse LBD • Authors employed the US Caucasian control group (n = 99) from a previous study (Farrer 2009) to compare the frequency of GBA1 mutations in the diffuse LBD group vs controls	All cases were sequenced for the 11 exons and exon-intron boundaries for the GBA1 gene	• GBA1 mutations identified in 6.8% (4/59) of cases with a pathological diagnosis of diffuse LBD • The frequency of GBA1 mutations in diffuse LBD was higher than that of normal controls (1.0%), albeit not statistically significant (P = 0.07; OR = 7.3; IC95% 0.8–65.4)
Farrer, 2009 (Farrer et al., 2009)	Case-control	3	200	Epidemiology	Assess the frequency of GBA1 mutations in a sample of neuropathologicallyconfirmed LBD and autopsy confirmed controls	• 101 cases with pathologic features consistent with LB disorders. Half had a prior clinical diagnosis of PD and included both brainstem LBD (n=34) or transitional LBD (n=17). Half had a prior clinical diagnosis of DLB, with autopsy confirmed DLBD (n=50) • 99 controls	Full sequencing of GBA1 coding region	GBA1 mutations identified in 101 neuropathologically defined LBD cases (3%) compared to 99 healthy post-mortem controls (1%); OR 3.0 (IC95% 0.3 – 29, p=0.3). All three affected carriers were classified as diffuse LBD (n=3/50; 6%)
Gamez Valero, 2016 (Gámez-Valero et al., 2016)	Case-control	3	305	Epidemiology Clinical presentation and prognosis	Explore the role of GBA1 mutations in Spanish DLB patients	•Neuropathological cohort: 50 DLB, 43 PD, and 34 control brains • Clinical cohort: 47 DLB patients and 131 controls	Analysis of 3 fragments of GBA1 cDNA containing the coding sequence	• 16 GBA1 mutation carriers identified, 5 of which were brains with pure DLB • The most common mutation, E326K, was strongly associated with pure DLB and PD with dementia • GBA1 mutations were overrepresented in men and associated with earlier DLB onset

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Straniero, 2020 (Straniero et al., 2020)	Case-control	3	12680	Epidemiology	Provide a variant-specific estimate of incidence, penetrance, sex distribution, and association with dementia of the 4 most common PD-associated GBA1 variants	4,923 Italian unrelated patients with primary degenerative parkinsonism (including 3,832 PD) enrolled in a single tertiary care center and 7,757 ethnically matched controls	• Screening of the p.E326K, p.T369M, p.N370S, and p.L444P variants • Estimation of incidence, penetrance, sex distribution and association with dementia of 4 GBA1 variants	• L444P variant most strongly associated with disease risk for PD, PD dementia, and DLB (OR for PD 15.63, IC95% 8.04–30.37, P = 4.97×10^−16; OR for PD dementia 29.57, IC95% 14.07–62.13, P = 3.86×10^−19; OR for DLB 102.7, IC95% 31.38–336.1, P = 1.91×10^−14) • High risk for dementia conferred by p.E326K (OR for PD dementia 4.80, IC95% 2.87–8.02, P=2.12×10^−9; OR for DLB 12.24, IC95% 4.95–30.24, P= 5.71×10^−8)
van der Lee, 2021 (van der Lee et al., 2021)	Case-control	3	2742	Epidemiology	Test if genetic variants in part explain the heterogeneity in DLB	• 190 probable DLB patients and 2,552 controls • p-tau/Aβ1–42 ratio in CSF was used to separate DLB cases into DLB with concomitant AD pathology (DLB-AD) or DLB without AD (DLB-pure)	• Assessment of variants previously associated with DLB (near APOE, GBA1, and SNCA) and polygenic risk scores for AD (AD-PRS) and PD (PD-PRS) • Study of clinical measures: age, MMSE, presence of core symptoms at diagnosis and disease duration	• All studied genetic factors associated with DLB risk: APOE4 (OR = 2.5, P= 4.5×10^–14), GBA1 (OR = 4.7, P = 1.6×10^–13), and SNCA (OR = 1.4, P= 1.1×10^–2) • APOE4 and the AD-PRS associated specifically with DLB-AD, but less with DLB-pure • GBA p.E365K variant strongly associated with DLB-pure (8.8-fold [P = 1.4×10^–16]) increased risk) and less with DLB-AD (3-fold [P= 2.9×10^–3] increased risk)• APOE4 associated with reduced MMSE, higher odds to have fluctuations and shorter disease duration • GBA p.E365K variant reduced the age at onset by 5.7 years
Shiner, 2021 (Shiner et al., 2021)	Case-control	3	100	Epidemiology Clinical presentation and prognosis	Explore the clinical impact of mutations in the GBA1 gene and APOE polymorphisms separately and in combination, in a cohort of AJ patients with DLB	100 consecutively recruited AJ patients with clinically diagnosed DLB	• Genotyping for GBA1 mutations and APOE polymorphisms • Cognitive and motor clinical assessments	• 32% DLB patients carriers of GBA1 mutations and 33% carried an APOE4 allele • GBA1 mutation carriers had a younger age of onset (mean [SD] age, 67.2 years [8.9] vs 71.97 [5.91]; P=0.03), poorer cognition assessed by the MMSE (21.41 [6.9] vs 23.97 [5.18]; P<0.005), and more severe parkinsonism assessed with the UPDRS III (34.41 [13.49] vs 28.38 [11.21]; P=0.01) compared to non-carriers • Patients carrying both a mild GBA1 mutation

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Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Irwin, 2017 (Irwin et al., 2017)	Retrospective cohort	3	213	Human neuropathology	Identify genetic and pathological markers that have the strongest association with survival and the interval between onset of motor symptoms and dementia in LBD	213 autopsy-confirmed LBD patients	Sequencing of the entire GBA1 coding region and all intron-exon boundaries to detect known mutations and the p.E326K variant	and the APOE4 allele (n=9) had more severe cognitive (P=0.048) and motor dysfunction (P=0.037) • Decreasing frequency of heterozygous patients carrying the GBA E326K risk allele or GBA1 mutation with increasing levels of AD neuropathology (P=0.03, both)
Tsuang, 2012 (Tsuang et al., 2012)	Case-control	3	953	Human neuropathology	Determine whether GBA1 influences risk of dementia with LBD neuropathologic changes (LBDNCs), AD neuropathologic changes (ADNCs), or both	• 391 controls and 562 autopsied cases with dementia • N=80 pure dementia with Lewy bodies [pDLB] = LBDNCs and no or low levels of ADNC • N=231 LBD-AD = LBDNCs and high-level ADNCs • N=251 AD = high-level ADNCs but without LBDNCs	Screening of the entire GBA1 coding region for mutations	• Pathogenic GBA1 mutations identified in 6 of 79 pDLB cases (7.6%), 8 of 222 LBD-AD cases (3.6%), 2 of 243 AD cases (0.8%), and 3 of 381 controls (0.8%) • Subjects with pDLB and LBD-AD were more likely to carry mutations than controls (pDLB: OR: 7.6; IC95% 1.8–31.9; P=0.006; LBD-AD: OR 4.6; IC95% 1.2–17.6; P=0.025), but there was no difference in frequencies between the AD and control groups (OR 1.1; IC95% 0.2–6.6; P=0.92) • Highly significant trend test across groups, with the likelihood of carrying a GBA1 mutation increasing in the following direction: control/AD < LBD-AD < pDLB
Goker-Alpan, 2010 (Goker-Alpan et al., 2010)	Case-control	3	14	Human neuropathology	Explore the contribution of GCase to the development of parkinsonian pathology	7 brain samples from subjects carrying GCase mutations with pathologic diagnoses of PD and/or LBD and 7 controls without GBA1 mutation but with similar neuropathological diagnoses	Assessment of GCase immunoreactivity in each LB, by immunofluorescent study	•Immunofluorescence studies on brain tissue samples from patients with parkinsonism associated with GCase mutations showed that GCase was present in 32–90% of LBs (mean 75%), some ubiquitinated and others non-ubiquitinated • In samples from 7 subjects without mutations, <10% of LBs were GCase positive (mean 4%)
Kurzawa-Akanbi, 2012 (Kurzawa-Akanbi et al., 2021)	Case-control	3	12	Human neuropathology	Evaluate the effects of mutant GBA1 gene in human frontal cortex tissue	Analysis of post-mortem frontal cortex tissue from 7 GBA1 mutation carriers with LBD, 5 GBA1 mutation carriers with no signs of neurological disease and human neural stem cells exposed to a GCase inhibitor	Assessment of GCase protein levels and activities, evaluation of lysosomal changes in frontal cortex tissue	GBA1 heterozygotes showed modest reduction of GCase protein (20% reduction) and enzyme activity (25% reduction) in the frontal cortex tissue irrespective of disease state, retention of GCase isoforms within the

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Perez-Roca, 2018 (Perez-Roca et al., 2018)	Case-control	3	125	Human neuropathology Assessment and diagnosis	1) Assess if GCase deficiency in LBD starts at the transcriptional level; 2) if possible brain GBA1 expression changes are also detectable in blood of LBD patients; 3) if alternative GBA1 splicing is dysregulated	• Brain samples from 20 DLB, 25 PD and 17 control brains • Blood samples of 20 DLB, 26 PD patients and 17 controls	Analysis of 3 GBA1 transcript variants (GBAtv1, GBAtv2 and GBAtv5) in brain and blood	endoplasmic reticulum and abnormal lysosomal activity • In brain, specific expression profiles identified in DLB temporal cortex and in PD caudate nucleus. In the temporal cortex, GBAtv1 expression was diminished in DLB (pure and DLB-AD) but not in PD. GBAtv5 was almost 4-fold decreased in pure DLB compared to PD and controls. In caudate nucleus, GBAtv1 was diminished in PDD and in DLB but not in PD without dementia. • In blood, significant GBAtv1 mRNA diminution found in both DLB and PD. In DLB, lowest GBAtv1 levels detected in patients with earliest onset.
Moors, 2019 (Moors et al., 2019)	Case-control	3	45	Human neuropathology	Gain more insight into changes in lysosomal activity in different brain regions of sporadic PD and DLB patients, screened for GBA1 variants	Cohort of patients with advanced PD and DLB as well as age-matched non-demented controls (n = 15/ group)	• Assessment of enzymatic activities of GCase, β-hexosaminidase, and cathepsin D in frontal cortex, putamen, and SN, using fluorometric assays • GBA1 variants screening	• Decreased activity of GCase (− 21%) in the SN of PD and DLB patients • Decreased activity of cathepsin D (− 15%) in the frontal cortex of PD and DLB patients • Population stratification was applied based on GBA1 genotype, showing substantially lower GCase activity (~ − 40%) in GBA1 variant carriers in all regions
Clark, 2015 (Clark et al., 2015)	Case-control	3	231	Human neuropathology	Investigate whether variants in lysosomal storage disorder genes other than GBA1 also contribute to LB pathology	231 brain autopsies included neuropathologically defined LBD without AD changes (n = 59), AD without significant LB pathology (n = 71), AD and LB variant (ADLBV) (n = 68), and control brains without LB or AD neuropathology (n = 33)	• Genetic analysis of 4 lysosomal storage disorder genes including GBA1, HEXA, SMPD1, and MCOLN1 in 231 brain autopsies, followed by 'gene wise' genetic association analysis. • Measurement of GCase activity in a subset of brain samples (n = 64) • Lipidomic analysis in brain autopsies (n = 67)	• In a 'gene-wise' analysis, variants in GBA1, SMPD1 and MCOLN1 were associated with LB pathology (P range: 0.03–4.14 ×10-5) • Mean levels of GCase activity lower in GBA1 mutation carriers vs non-carriers (P<0.001) • Significant increase and accumulation of several species for the lipid classes, ceramides and sphingolipids, observed in LBD brains carrying GBA1 mutations vs controls (P range: p<0.05-p<0.01)
Gündner, 2019 (Gündner et al., 2019)	Case-control	3	45	Human neuropathology	Characterize the interrelation between GCase and α-synuclein in human brain tissue to explore mechanisms underlying GBA1-associated PD	Brain tissue samples from frontal cortex, putamen and SN of PD (n=15) and DLB (n=15) patients and age-	• Quantitative immuno-based assays on brain tissue samples to measure GCase and α-synuclein (total and phosphorylated p-129) protein levels • Liquid	• Inverse correlation between reduced GCase enzyme activity and protein levels with increased glucosylsphingosine levels • In the SN, significant

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
						matched non-demented controls (n=15)	chromatography–mass spectrometry method for the detection of the GCase lipid substrate glucosylsphingosine • Assessment of GBA1 variant carrier status	correlation between GCase protein reduction and increased p129/total α-synuclein ratios • GBA1 variants were strongly related to reduced GCase levels. For the SN, 21% reduction in GCase protein levels in the PD-DLB group and 39% reduction in the PD-DLB + GBA1 subgroup carrying GBA1 variants • Confirmatory path analysis: GCase dysfunction impacts PD-DLB status by increasing α-synuclein ratios in the SN, which is partly mediated by increasing glucosylsphingosine levels
Kurzawa-Akanbi, 2021 (Kurzawa-Akanbi et al., 2021)	Case-control	3	129	Human neuropathology	To investigate relationships between LBD specific GCase deficits, GBA1-related pathways, and SNCA levels in human brain tissue	• 64 samples of post-mortem frontal cortex, 50 samples of cingulate cortex from matched LBD, LBD with heterozygous GBA1 mutations, controls with and without heterozygous GBA1 mutations • Post-mortem CSF samples (n=15) from LBD with and without GBA1 mutations, and controls	Assessment of extracellular vesicles derived from post-mortem CSF and brain tissue from GBA1 mutation carriers and non-carriers	Extracellular vesicles purified from LBD CSF and frontal cortex were heavily loaded with ceramides and neurodegeneration-linked proteins including SNCA and tau, with an elevation of ceramides irrespective of GBA1 mutation status
Goker-Alpan, 2008 (Goker-Alpan et al., 2008)	Prospective case series	4	10	Clinical presentation and prognosis	Define the clinical and neurologic spectrum of parkinsonian manifestationsassociated with GBA1 mutations	10 consecutive GBA1 mutation carriers with parkinsonism	• Identification of GBA1 genotypes by DNA sequencing • Physical and neurologic examinations, UPDRS III, disease staging Hoehn and Yahr criteria, autonomic nervous system function, MMSE, mood and behavior evaluation, olfaction (UPSIT), in all patients • Neuropsychometric and neuro-ophtalmologic evaluation (n=7) • 21-channel EEG (n=8)	• Genotyping identified GBA1 mutations N370S, L444P, and c.84dupG and recombinant alleles • Mean age at onset of parkinsonian manifestations: 49 years (range, 39–65 years), disease duration: 7.8 years (range, 1.2–16.0 years), UPDRS III score: 26.3 (range, 13–38) • Half of the patients reported cognitive changes later in the disease course. Six patients were diagnosed as having PD, 3 as having DLB and 1 as having a "Parkinson plus" syndrome • Most frequent nonmotor finding: olfactory dysfunction • 5 patients reported symptoms of dysautonomia • Atypical manifestations included myoclonus, EEG abnormalities, and seizures

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Bregman, 2019 (Bregman et al., 2019)	Case-control	3	64	Clinical presentation and prognosis	Explore the influence of GBA genotype in AJ patients with DLB on the performance in phonemic and semantic verbal fluency tasks, compared to AD	44 DLB and 20 AD	Assessment of performance in phonemic and semantic verbal fluency tasks	Patients with DLB who carried GBA mutations scored more poorly than patients with AD in the phonemic task, whereas DLB-noncarriers performed similarly to patients with AD.
Lerche, 2019 (Lerche et al., 2019)	Case-control	3	139	Clinical presentation and prognosis Assessment and diagnosis	Explore whether GBA1 mutations are associated with a CSF α-synuclein profile in DLB	100 DLB and 39 controls	• Screening of GBA1 gene and single nucleotide polymorphisms in SNCA rs356220, APOE rs429358, and MAPT rs1052587 • CSF levels of total α-synuclein, Aβ1–42, total-Tau, p-Tau, neurofilament light chain • GBA1-subgroup classification done according to established mutational severity in PD (unknown significance vs. mild pathogenic vs. severe pathogenic mutation)	• Severity of GBA1 mutations associated with younger age at onset and higher RBD prevalence • CSF levels of total alpha-synuclein were lowest in DLBGBA_pathogenic compared to DLBGBA_mild and DLBGBA_wildtype
Parnetti, 2009 (Parnetti et al., 2009)	Case-control	3	80	Assessment and diagnosis	Investigate pattern of lysosomal hydrolases in differentneurodegenerative conditions, including synucleinopathies and tauopathies	DLB (n=17), AD (n=20), Fronto-Temporal Dementia (n=20) and controls (n=23)	Assessment of the activity of α-mannosidase, β-mannosidase, β-glucocerebrosidase, β-galactosidase and β hexosaminidase in cerebrospinal fluid	• Alpha-mannosidase activity showed a marked decrease across all the pathological groups as compared to controls • β-glucocerebrosidase activity was selectively reduced in DLB CSF
Usenko, 2022 (Usenko et al., 2022)	Case-control	3	396	Assessment and diagnosis	Assess changes in activities of enzymes involved in ceramide metabolism in patients with different synucleinopathies	163 PD, 44 DLB, 30 MSA and 159 controls	GCase, α-galactosidase, acid sphingomyelinase enzyme activities, and concentrations of substrates (hexosylsphingosine, globotriaosylsphingosine, lysosphingomyelin) measured by liquid chromatography tandem-mass spectrometry in blood	• Increased hexosylsphingosine concentration in DLB and MSA in comparison to PD and controls ($p < 0.001$), associated with earlier age at onset of DLB ($p = 0.0008$) • Acid sphingomyelinase activity was decreased in DLB, MSA patients compared to PD patients ($p < 0.0001$, $p < 0.0001$, respectively)
Clinical Trial Identifier: NCT05304195 (Assistance Publique - Hôpitaux de Paris, 2022)	Case-control	3	236	Assessment and diagnosis	Explore GCase activity to identify a subpopulation eligible for a therapeutic trial in DLB	118 DLB and 118 controls	• Comparison of GCase activity between patients and controls • Search for variants or mutations of the GBA gene and correlation with GCase activity • Correlation between clinical characteristics (UPDRS motor scale, MMSE) and GCase activity in patients	NA
Clinical Trial Identifier NCT04405596 (Pasternak, 2022)	Phase 1/2 Placebo/ control Double-blind Randomized study	1	15	Treatment	Investigate whether the medication Ambroxol is safe, effective and well tolerated for the treatment of DLB	• N=15 DLB subjects • Study will last 52 weeks • Estimated Primary Completion Date: September 2023	• Clinical, neuropsychological, neuroimaging, biological (CSF, blood, urine) assessments • Measurement of adverse events	NA

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Table 1 (*continued*)

Study (1st Author, Year) [Ref]	Study Type	Quality Rating*	N	Manuscript section	Objective	Subjects	Main Outcome Measures	Main results
Clinical Trial IdentifierNCT04588285 (Helse Fonna, 2021)	Phase 2a Placebo/ control Double-blind Randomized study	1	172	Treatment	Investigate if the medication Ambroxol is safe, effective and well tolerated for the treatment of early DLB	• N=172 subjects with prodromal and mild DLB • Study will last 18 months + extension • Estimated Primary Completion Date: April 2022	• Cognitive, Neuropsychiatric and Functional Outcomes • ECG and blood analysis • Measurement of adverse events	NA

Abbreviations: AD=Alzheimer's disease; ADLBV=AD and LB variant; ADNCs=Alzheimer disease neuropathologic changes; AJ=Ashkenazi Jews; CSF=Cerebrospinal fluid; DLB=Dementia with Lewy bodies; GDS = Geriatric Depression Scale; LB=Lewy Body; LBD=Lewy Body Disease; LBNPCs=LBD neuropathologic changes; MMSE=Mini-Mental State Examination; MSA=Multiple system atrophy; NA=Not Applicable; N-subj= Total number of subjects; OR=odds-ratio; PD=Parkinson's disease; RBD = Rapid Eye Movement Sleep Behavior Disorder; SN= substantia nigra.

included a small number of patients and have explored different biomarkers preventing comparability of the data. In 2019, Lerche et al. (2019) showed decreased CSF levels of total SNCA in DLB presenting a severe pathogenic GBA1 mutation compared to DLB patients with a mild mutation and non-carriers. In a neuropathological study, Perez-Roca et al. (2018) have shown that early-onset DLB patients had lowest levels of GBA1 transcript variants (GBAtv1) in blood. In 2022, Usenko et al. (2022) demonstrated pronounced alterations of lysosomal activities measured by liquid chromatography tandem-mass spectrometry in blood in patients with DLB. An on-going study (EGELY) (Assistance Publique - Hôpitaux de Paris, 2022) aims to determine if GCase activity is decreased in the blood of DLB patients to identify a subpopulation eligible for a therapeutic trial.

3.2.2. Treatment

So far, no curative or symptomatic treatments have been validated in DLB-GBA1 mutation carriers. Two on-going clinical trials are evaluating the safety and efficacy of Ambroxol in DLB, including genetic analysis of GBA1 gene. Both studies are presented in Table 1 (Pasternak, 2022; Helse Fonna, 2021).

4. Discussion

In this review, we have synthetized current clinical research evidence in GBA1-associated DLB. Clinical research confirmed the strong association between GBA1 mutations and DLB and suggests that GBA1 mutation carriers present a more severe phenotype across the spectrum of LB disorders, with an earlier age at symptom onset, more severe motor and cognitive dysfunction, more visual hallucinations and REM sleep disorders. Neuropathological studies show that GBA1 mutations are associated with pathologically "purer" LB disorders, characterized by a more diffuse pattern of LB distribution involving the cerebral cortex, and less severe AD pathological findings. Few studies have assessed potential biological biomarkers in DLB subjects with a GBA1 mutation. No therapeutics have been validated yet for GBA1-associated DLB and clinical trials assessing treatments that increase GCase activity are just starting in DLB patients.

Several epidemiologic studies have confirmed that GBA1 gene mutations were linked to an increased risk of DLB. However, the frequency of GBA1 mutations was highly variable, possibly due to various genetic methods from exploration of GBA1 mutations to full genotyping and to the exploration of different populations. Data are consistent in Ashkenazi Jews who seems at higher risk of GBA1 mutations and LB pathology. Larger studies from general population would be needed but the diagnostic difficulty and the lack of diagnostic accuracy in epidemiological cohorts preclude such studies for the time being. Such studies, in alive patients, could be done in more specific cohorts like ADNI (Weiner and Veitch, 2015), EPAD (Ritchie et al., 2020), BALTAZAR (Hanon et al., 2018), PPMI (Parkinson Progression Marker Initiative, 2011) and French MEMENTO Cohort (Dufouil et al., 2017).

The results of all clinical and neuropathological studies are consistent and suggest a more severe phenotype and more and purer LB brain load in DLB patients carrying a GBA1 mutation. However, all studies have some limitations mainly the lack of longitudinal follow-up and all except one (Irwin et al., 2017) explored small cohort size. Interestingly, even if the evidence base in DLB is still limited, results of all studies are concordant with the results of similar studies exploring GBA1 mutations in PD. These findings suggest that GBA1 mutations and impaired GCase activity are aggravating factors for the pathophysiology and symptoms of alpha-synucleinopathies, particularly in psychiatric and cognitive clinical forms.

Similarly, neuropathological studies have demonstrated that GBA1 mutations seem to be an aggravating factor for decreased brain GCase protein levels and GCase enzyme activity. However, studies have also described that the levels of GCase protein and enzyme activity were reduced in DLB patient non-carriers of GBA1 mutations, confirming the

hypothesis that there is a link between synucleinopathy and GCase but also that GBA1 mutations are probably not causative mutations but act as a confounding factor. Unfortunately, so far, there are few studies exploring biomarkers in alive patients in order to explore the link between GCase, brain and DLB. These kinds of studies would be required to validate GCase protein or activity level as a diagnosis and companion biomarker in case of treatment targeting GCase and efficient in DLB.

Lower GCase activity in CSF and brain samples of PD and DLB patients suggests a causal role of the lysosomal enzyme in these synucleinopathies. Preclinical research demonstrated that GBA1 mutants induce SNCA accumulations in a dose- and time-dependent manner (Cullen et al., 2011). Moreover, in synucleinopathy models, the activation of GCase, the use of glucosylceramide synthase inhibitors or acid ceramidase inhibitors all resulted in reduced accumulation of pathological SNCA (Sardi et al., 2017; Mazzulli et al., 2016; Kim et al., 2018). *In vitro* and in vivo studies have reported that the pharmacological chaperone for GCase Ambroxol increases GCase enzyme activity and reduces SNCA levels. As in Gaucher Disease, other therapeutic approaches have to be considered including substrate reduction therapy with the glucosylceramide synthase inhibitor Venglustat and gene-replacement therapy PR001A to deliver a functional copy of the GBA1 gene to the brain. Venglustat development was stopped for PD in 2021 after the Phase 2 trial MOVES-PD missed its primary endpoint (Sanofi, 2022), but PR001A is currently tested in PD (Prevail Therapeutics, 2022) and should be tried in DLB. The design of such studies would be easy in phase I and II but become much difficult in phase III. As GBA1 mutations appear as aggravating factors and as DLB clinical symptoms are variable according to patients, it will be difficult to define a precise and common primary clinical outcome for the efficacy of treatment. The design would probably require a homogenous population with the same phenotype profile in order to target specific symptoms.

Exploring the link between GBA1 mutations and DLB is a recent area of interest, with a limited number of preclinical and clinical studies in this field. Moreover, most clinical studies are case-control studies, with therefore a low quality of evidence. Future studies should precise the phenotype of GBA1-associated DLB, with longitudinal follow-up and neuropathological confirmation of the diagnosis. Further studies are needed to investigate the mechanisms by which GBA mutations may impact the natural history of DLB. This would help to confirm that GCase-based biological biomarkers (GCase activity or GBA1 transcript variants) could be valuable diagnostic biomarkers for DLB. Clinical trials are needed to best bring forward therapies to treat GBA1-associated DLB.

No clinical practice guidelines yet exist for GBA1 gene screening in patients meeting diagnostic criteria for DLB (McKeith et al., 2017). No clinical sign is specific of GBA1 mutations, but based on this review, an early symptom onset, a familial history of parkinsonism or GD, an initially severe motor and cognitive dysfunction or early psychosis should raise the possibility of a GBA1 mutation.

5. Conclusions

After the initial discovery of the role of GBA1 mutations and lysosomal impairment in the accumulation of SNCA and development of PD, evidence has emerged regarding the strong association between GBA1 mutations and DLB. Research work is still very recent in this field and contributes progressively to a better understanding of the pathogenesis of DLB. Hopefully, future studies will bring about improved phenotyping of GBA1-associated DLB, discovery of new biomarkers and effective therapeutic approaches.

Data availability

We present a review and use the already published data from other articles.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104856.

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