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REVIEW ARTICLE

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Glucocerebrosidase mutations and neuropsychiatric phenotypes in Parkinson's disease and Lewy body dementias: Review and meta-analyses

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Heterozygous mutations in glucocerebrosidase gene (*GBA*) are a major genetic risk factor for Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Recently, there has been a considerable focus on the relationship between *GBA* mutations and emergence of cognitive impairment and neuropsychiatric symptoms in these diseases. Here, we review the literature in this area, with a particular focus, including meta-analysis, on the key neuropsychiatric symptoms of cognitive impairment, psychosis, and depression in Parkinson's disease. Our meta-analysis demonstrated that *GBA* mutations are associated with a 2.4-fold increased risk of cognitive impairment. In addition, our novel meta-analyses of psychosis and depression showed a 1.8- and 2.2-fold increased risk respectively associated with *GBA* mutations, although due to possible bias and heterogeneity the depression findings should be interpreted with caution. While the precise mechanisms which increase susceptibility to neurodegeneration in *GBA* carriers are not known, evidence of greater cortical Lewy body pathology, reduced patterns of cortical activation, and hippocampal pathology in animal models are all consistent with a direct effect of *GBA* mutations on these symptoms. Extension of this work in DLB and individuals without neurodegeneration will be important in further characterizing how *GBA* mutations increase risk for PD and DLB and influence disease course.

KEYWORDS
depression, *GBA*, psychosis

1 | INTRODUCTION

Homozygous mutations in the gene encoding the lysosomal enzyme glucocerebrosidase (GCase), *GBA*, cause the lysosomal storage disorder Gaucher disease (GD). There are a vast range of symptoms associated with GD, it being broadly categorized into type 1 (accounting for >90% of cases) and types 2 and 3. There is some evidence of neuropsychiatric deficits, including cognitive deficits in visuospatial domains, in GD but these are not a cardinal feature of the disease (Staretz-Chacham, Choi, Wakabayashi, Lopez, & Sidransky, 2010). Traditionally types 2 and 3 were the only variants of GD thought to have neurological involvement but the observation of parkinsonism in type 1 GD led to *GBA* mutations becoming an area of intense interest in the field of neurodegeneration (Neudorfer et al., 1996). Indeed, heterozygous mutations are now known to be one of the most common genetic risk factors for Parkinson's disease and dementia with Lewy bodies (DLB) (Nalls et al., 2013; Neumann et al., 2009). Both PD and DLB are associated with a high frequency of neuropsychiatric symptoms, which are often debilitating and associated with poor quality of life (Aarsland et al., 2007; Todorova, Jenner, & Ray Chaudhuri, 2014) but their underlying biology is only partially understood. Thus, elucidating the underlying mechanisms associated with these symptoms is now seen as vital to the wider understanding of these diseases and their clinical management.

An important step in understanding the aetiology of neuropsychiatric symptoms associated with DLB and PD and the extent to which they overlap with each other will be the identification of genetic risk factors associated with the poor prognosis related to these symptoms.

In this article, we review the current literature around the role of *GBA* mutations in neuropsychiatric phenotypes common in PD, with a particular focus on cognitive impairment, psychosis, and depression. The emerging evidence in DLB is also reviewed.

1.1 | Structure and function of *GBA*

The first study reporting mutation frequency of *GBA* in PD studied the occurrence of six of the most common mutations in idiopathic PD, Alzheimer's disease (AD) and healthy Ashkenazi Jewish populations. Mutations in *GBA* were found in 31.3% of PD patients, compared to 4% of AD patients, and 6.2% of healthy controls (Aharon-Peretz, Rosenbaum, & Gershoni-Baruch, 2004). In idiopathic PD, excluding Ashkenazi Jewish populations, the frequency of *GBA* mutations lies between 3.21% (Choi et al., 2012) and 21% (Lwin, 2004) when sequencing the whole gene. The most common GD-causing mutations are N370S and L444P although this differs by ethnicity (Barkhuizen, Anderson, & Grobler, 2016). *GBA* mutations can be classified as severe/neuropathic or mild/non neuropathic based on their causal role in type 2/3 and type 1 GD respectively. L444P is a neuropathic mutation while N370S is a non neuropathic mutation. Other variants which do not cause GD or whose clinical phenotype is unknown are also present in the gene. Two notable examples are E326 K and T369M, neither of which cause GD but E326 K is associated with PD while the role of T369M is unclear (Mallett et al., 2016). It is therefore evident that examination of *GBA*-related risk for Lewy body diseases and associated neuropsychiatric symptoms should extend beyond those GD causing variants.

The number of mutations reported in *GBA* which are linked to GD has exceeded 300 including missense, nonsense, frame-shift, and splice site mutations. The gene itself was localized to 1q21 in 1985 (Ginns et al., 1985). *GBA* spans 7.6 kb of genomic DNA divided into 11 exons. A highly homologous transcribed but non functional pseudogene, *GBAP*, is located 16 kb downstream from *GBA*, containing the same organization of exons. Due to the combination of 96% exonic sequence homology and proximity, recombination events are facilitated contributing to the creation of mutant alleles (Hruska, LaMarca, Scott, & Sidransky, 2008).

GCase is a membrane associated lysosomal hydrolase enzyme, the mature form of which is comprised of 497 amino acids and has molecular weight of approximately 60 kDa depending upon glycosylation (Horowitz et al., 1989). Structurally, GCase is comprised of 3 distinct domains. Domains I and II are non catalytic and predominantly consist of a major three stranded anti-parallel β-sheet and two closely associated β-sheets not unlike an immunoglobulin fold, respectively. Although these domains are non catalytic and the functions are not fully understood, the location of several mutations throughout these domains suggest an important regulatory role. Domain III contains the $(\beta/\alpha)_8$ (TIM) barrel catalytic site. Residue Glu235 serves as the acid/base and Glu340 as the nucleophile in the catalytic cycle (Kacher et al., 2008).

GCase is translated in endoplasmic reticulum (ER) bound polyribosomes to a 56 kDa polypeptide, from where it is translocated through the ER. Passage through the ER is accompanied by cleavage of a leader sequence and N-linked glycosylation of four asparagine resides. High mannose sugars are further modified as GCase moves through the Golgi apparatus (Erickson, Ginns, & Barranger, 1985). GCase is further modified via sugar residues in the Golgi before being trafficked to the lysosome as a mature protein by a mannose 6 phosphate receptor independent pathway utilizing the GCase specific receptor, LIMP-2 (Erickson et al., 1985; Reczek et al., 2007).

1.2 | *GBA*-related neurodegenerative disease mechanisms and pathology

Although there is good evidence linking *GBA* mutations with a variety of neuropsychiatric phenotypes in PD and other diseases the mechanisms underlying these associations are not yet clear. Both loss of- and gain of function hypotheses have been proposed to explain the mechanistic link between *GBA* mutations and the expression of synucleinopathies, which have been reviewed extensively elsewhere (Barkhuizen et al., 2016; Sidransky & Lopez, 2012). Briefly, gain of function hypotheses center upon the association between *GBA* mutations and alpha-synuclein aggregation, while loss of function hypotheses are chiefly derived from the observation of deficiency in GCase activity. It is important to highlight that there is no unequivocal evidence to lead to the rejection of either of these hypotheses and the extent of contribution of each to PD and DLB susceptibility, or the aetiology of neuropsychiatric symptoms therein, is not known.

One study of *GBA*-related Lewy body pathology in autopsy confirmed pure DLB, AD-DLB, and pure AD cases found that pure AD cases were no more likely to carry mutations than controls (Tsuang et al., 2012). On the other hand, *GBA* mutations were much more likely to be found in individuals with pure DLB pathology followed by those with mixed DLB and AD but others have not found evidence of such a relationship (Parkkinen et al., 2011).

Consistent with a direct link between *GBA* mutations and neurodegeneration, a murine model of GD has been shown to exhibit memory deficits and hippocampal alpha-synuclein pathology in homozygous animals (Barkhuizen et al., 2016; Sardi et al., 2011). Heterozygous animals also exhibited increased alpha-synuclein aggregation when compared to wild-type but at around 50% of the level of homozygous mice. However, memory deficits as measured by the novel object recognition test were not present in heterozygous mice. Cognitive phenotype characterization in this mouse strain has yet to be done but will be an important avenue of future research.

While a mechanistic link between *GBA* mutations and disease phenotypes remains elusive and despite the conflicting reports from neuropathological studies, recent advances in stem cell technology have shed some light on possible links between *GBA* mutations and cellular changes which increase susceptibility to neurodegeneration. By differentiating induced pluripotent stem cells (iPSCs) into dopaminergic neurons carrying *GBA* mutations Schondorf et al. (2014) were for the first time able to demonstrate a direct link between *GBA* mutations and extra-cellular alpha-synuclein levels. Later, Fernandes Hugo et al. (2016) describe a series of disrupted lysosomal processes, resulting in an increase in extra-cellular alpha-synuclein. More recently, and providing

a link between *GBA* mutations and alpha-synuclein in vivo, glucocerebrosidase activity in blood was found to be reduced, and plasma oligomeric alpha-synuclein elevated, among mutation carriers compared with non carriers (Pchelina et al., 2017).

Thus, initial work does indicate more rapid development of cortical pathology, and a more detailed understanding of specific differences in molecular processes and whether these create opportunities for precision medicine interventions will be an important area of development going forward.

2 | RELATIONSHIP BETWEEN *GBA* MUTATIONS AND NEUROPSYCHIATRIC PHENOTYPES IN PD

There has been a considerable focus on the relationship between *GBA* mutations and disease course in PD, including motor, non motor, and neuropsychiatric symptoms, the latter of which will be the focus of the majority of the remainder of this review. We used the search terms "*GBA* OR glucocerebrosidase AND psycho* OR delusion* OR hallucinat* OR neuropsych* OR non motor OR agitation OR depression OR mood OR dementia OR cogniti*." Manual search of the references of the aforementioned reviews and articles generated by our own search was undertaken as well. The search was first conducted on December 21st, 2016 with a further update carried out on January 31st, 2017. We also conducted meta-analyses where possible and phenotypes where too few studies were available for meta-analysis are instead descriptively reviewed. We applied the following general criteria and additional criteria specific to each phenotype listed under the appropriate headings below, with the resultant studies taken forward for meta-analysis:

Inclusion criteria:

- Diagnosis of idiopathic PD.
- Written in English.

Exclusion criteria:

- Studies restricted to familial PD only.

All analyses were carried out in Stata version 14 using random effects models. Heterogeneity was assessed by examination of the I^2 and the chi-squared statistic following the Cochrane review guidance for identifying and measuring heterogeneity. Studies not meeting inclusion criteria for the meta-analysis are listed, with reasons for exclusion, in supplementary Table S1.

By far the most frequent GD-related mutations detected among the studies included for meta-analysis were L444P and N370S. Variants of unknown pathological function in GD were detected in many studies as well but the most common of these were E326 K and T369M. Figure 1 depicts the variants detected among the studies included in the meta-analysis.

It should be noted that there were different strategies for inclusion of *GBA* variants in the studies reviewed. We took a broad approach, including any study detecting any number of mutations by any method (sequencing or genotyping). Some studies split out their analyses by grouping *GBA* variants according to their functional or pathogenic properties (Cilia et al., 2016; Crosiers et al., 2016; Jesús et al., 2016; Mata et al., 2016; Oeda et al., 2015). Where possible we included the data for the total variants rather than any sub groups (Cilia et al., 2016). Where only sub groups were provided we selected the group with pathogenic mutations (in these instances, the sub-groups not included in the meta-analysis are descriptively reviewed) (Jesús et al., 2016; Mata et al., 2016; Oeda et al., 2015). Crosiers et al. (2016) only focused on coding variants and did not analyze the effect of others (e.g., those in intronic regions).

2.1 | Cognition and dementia

Specific inclusion criteria:

- No exclusion criteria for cognitive impairment.
- Assessment of significant cognitive impairment either by operationalized criteria for MCI or dementia or by falling below specified cut-off on a standardized assessment tool.

Specific exclusion criteria:

- Cognitive impairment not treated as a dichotomous outcome variable.
- Frequencies of cognitive impairment not reported.

Recently, Zhang et al. (2015) conducted a meta-analysis examining the influence of *GBA* mutations on cognitive impairment in PD. They analyzed six studies (including their own new data) and found that *GBA* mutations were associated with a 3.2-fold increased risk of dementia or significant cognitive impairment. Since, this analysis there have been a large number of studies published addressing the same question, warranting an update.

Sixteen studies met the above criteria, but the cohorts used in three significantly overlapped (Chahine et al., 2013; Davis et al., 2016; Mata et al., 2016). We only included Mata et al. (2016) as this study has the largest sample size (supplementary Table S2). The study by Jesús et al. (2016) split *GBA* mutations by whether or not they were, in their terms, benign, or deleterious but an aggregate figure of the two was not reported. As the deleterious group included the two most common mutations in Caucasians, N370S, and L444P, and therefore most closely matched the mutations examined in other studies we used this group in our meta-analysis. This resulted a total of 450 *GBA* carriers and 6,111 non carriers over 13 studies being eligible for analysis (Alcalay et al., 2012; Brockmann et al., 2011; Cilia et al., 2016; Crosiers et al., 2016; De Marco et al., 2008; Jesús et al., 2016; Malec-Litwinowicz et al., 2014; Mata et al., 2016; Oeda et al., 2015; Seto-Salvia et al., 2012; Swan et al., 2016; Wang et al., 2014; Zhang et al., 2015).

Four studies classified cognitive impairment according to predefined cut-offs on validated measures of global cognition (MMSE or MoCA), eight used operationalized diagnostic criteria for

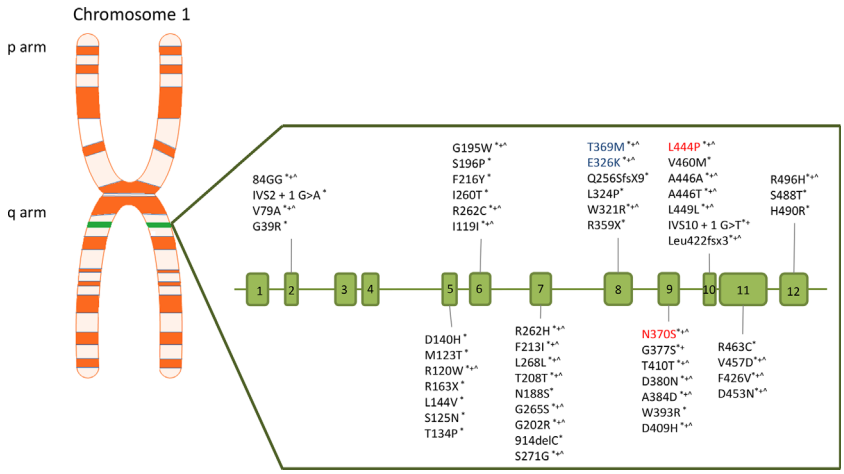

FIGURE 1 *GBA* variants reported by studies used in meta-analyses; * reported by studies included in cognition meta-analyses; + reported by studies included in psychosis meta-analyses; ^ reported by studies included in depression meta-analyses.

dementia according to either the Movements Disorders Society Task Force or DSM-IV and one used a clinical diagnosis (supplementary Table S3).

In our updated analysis *GBA* mutations were associated with a statistically significant 2.4-fold increased risk of cognitive impairment (OR: 2.4, 95%CI: 1.69–3.4, $p < 0.001$, Figure 2), confirming prior meta-analysis findings albeit with a slightly lower odds ratio estimate and in line with recent descriptive reviews (Aarsland et al., 2017). The associated funnel plot (supplementary Figure S2) did not show any evidence of bias but it should be noted that there was evidence of possible moderate heterogeneity in the studies analyzed ($I^2 = 40.2\%$; $\chi^2 = 20.08$, df = 12, $p = 0.066$). Meta-regression showed no evidence that diagnosis method (dementia or cut-off on an assessment scale), mutation screening method (sequencing or genotyping by PCR), disease duration or ethnicity influenced the effect of *GBA* mutation (data not shown).

The above analysis quantifies the extent to which *GBA* mutations are associated with cognitive impairment, defined by low score on a validated assessment scale or operationalized dementia criteria. Broader review of the literature paints a more nuanced picture whereby specific *GBA* mutations appear to have more severe effects than others and specific cognitive domains may be more affected than others.

2.1.1 | Progression to dementia/significant cognitive impairment

Three studies have conducted more in-depth evaluations of cognition in PD with respect to *GBA* mutations (Alcalay et al., 2012; Mata et al., 2016;

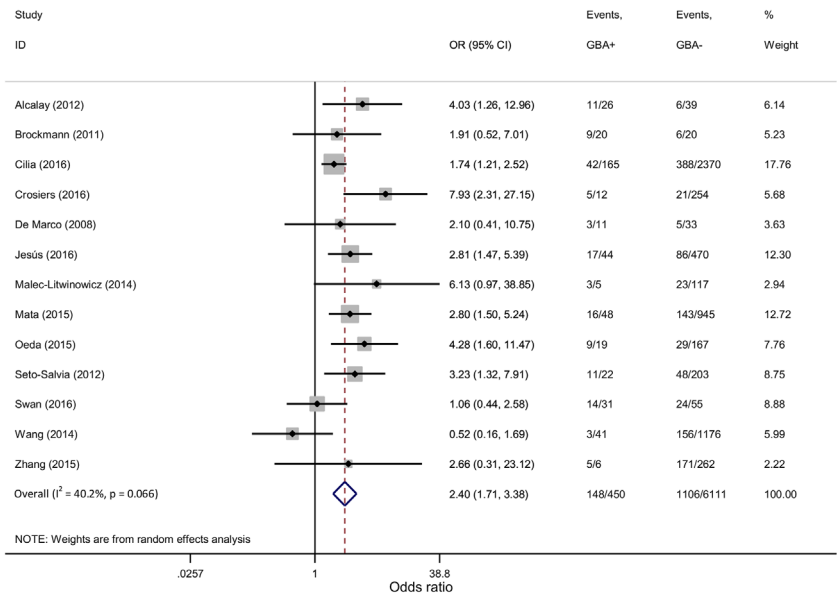

FIGURE 2 Forest plot of dementia/cognitive impairment associated with GBA mutations. GBA+, PD carrying GBA mutation; GBA−; PD not carrying GBA mutations.

Thaler et al., 2016; Zokaei et al., 2014). Across these there appears to be a relatively greater burden of impairment in visuospatial and executive function and working memory compared associated with *GBA* mutations. Mata et al. (2016) highlight a dissociation between deficits in the aforementioned domains affected by *GBA* mutations and those associated with *APOE4*, which are primarily early Alzheimer-type deficits in word list learning and verbal fluency.

A number of longitudinal studies have examined the role of *GBA* mutations on the natural history of PD with respective to cognitive impairment. Two small initial studies both found evidence that *GBA* mutations are associated with a shorter time to cognitive impairment in PD patients, assessed either prospectively (Winder-Rhodes et al., 2013) or retrospectively from case notes (Oeda et al., 2015). Over a shorter period of time Brockmann et al. (2015) also found *GBA* mutations to be associated with more rapid cognitive decline and subsequently two larger studies again using Cox proportional hazards models confirmed this association (Cilia et al., 2016; Jesús et al., 2016; Liu et al., 2016).

2.1.2 | Differential effects of GBA variants

Mata et al. (2016) analyzed E326 K separately to all other mutations but found a similar pattern of cognitive deficits. Crosiers et al. (2016) also detected E326 K but this was included in their analysis with other *GBA* variants so more work may be required to split out any unique effect. Conversely, in their benign variant group which included E326 K and T369M, Jesús et al. (2016) failed to find any associated with cognitive impairment and similarly Winder-Rhodes et al. (2013) report no significant association with progression to dementia in their longitudinal analysis. Although not GD-related, E326 K is a risk factor of PD but on the basis of evidence presented here more work needs to be done to elucidate any specific effect of non-GD-related variants. Beyond these common non-GD variants, Oeda et al. (2015) found 30 individuals carrying non synonymous variants not associated with GD and failed to find any associated with cognition at baseline (they did not examine this group with respect to time to dementia). Finally, there is compelling evidence that there are different strengths of effect within those variants associated with GD. Both Cilia et al. (2016) and Liu et al. (2016) showed that neuropathic *GBA* mutations (which include L444P) were more strongly associated with progression to dementia/global cognitive impairment when compared to non neuropathic mutations (which include N370S) and non-*GBA* carriers. Importantly, these findings were supported by functional neuroimaging showing that in PD severe mutation carriers the pattern of parietal and occipital activity, and DAT density, more closely resembled DLB while PD mild mutation carriers were more similar to PD non carriers. Along with the clinical observations, this suggests that among alpha-synucleinopathies *GBA* mutations give rise to similar phenotypes which may have important implications for treatment strategies in this cluster of disorders.

2.2 | Psychosis

Specific inclusion criteria:

- Assessment of hallucinations and/or delusions by standardized assessment tool or evaluation by specialist physician.
- Psychosis status dichotomized into those with symptoms and those without.

Specific exclusion criteria:

- Psychosis not treated as a binary variable.
- Frequencies of psychosis not reported.

Six studies met the inclusion criteria for the meta-analysis, totaling 219 PD patients with *GBA* mutations and 2,044 PD patients without (Aharon-Peretz, Badarny, Rosenbaum, & Gershoni-Baruch, 2005; Cilia et al., 2016; De Marco et al., 2008; Jesús et al., 2016; Oeda et al., 2015; Thaler et al., 2016), see supplementary Table S3. The study by Jesús et al. (2016) was again restricted to the mutations they classified as deleterious (see above). Two studies used part 1 of the UPDRS to classify psychosis, three classified by clinician review and the remaining one used the PD NMS Questionnaire (supplementary Table S3). The phenotype investigated ranged from a composite psychotic syndrome comprising delusions and/or hallucinations to a phenotype comprising hallucinations only. Where frequency of hallucinations and other psychotic symptoms were listed separately the frequency of hallucinations was analyzed.

GBA mutations were associated with a 1.83-fold increase in risk for psychosis (95%CI: 1.23–2.74, $p = 0.003$, supplementary Figure S3), confirming the relationship highlighted in previous descriptive reviews (Ffytche et al., 2017). There was a no evidence of significant heterogeneity or bias ($I^2 = 17.1\%$; $\chi^2 = 6.03$, df = 5, $p = 0.3$, Figure 3).

There were three studies which were not eligible for inclusion in the above meta-analysis: one found a much higher frequency of hallucinations among *GBA* carriers but the difference did not reach statistical significance, perhaps due to small sample size (excluded because psychosis frequencies were not reported) (Wang et al., 2014). A second found no evidence of association with psychosis as measured quantitatively by the Neuropsychiatric Inventory (excluded because symptom was measured on a quantitative scale) (Brockmann et al., 2011). The third study not included in the meta-analysis examined *GBA* mutations solely in familial PD, hence the exclusion (Li et al., 2014). Here, the authors report a similar association as found in the meta-analysis, suggesting the *GBA* phenotype extends to inherited forms of PD as well. Finally, another study did not directly compare or statistically test the difference between *GBA* carriers and non carriers but did observed a high rate of hallucinations in *GBA* mutations carriers (45%) (Neumann et al., 2009).

In the same study as their cognitive analysis described above, Oeda et al. (2015) also ran a Cox proportional hazards model to assess the impact of *GBA* mutations on time to psychosis onset in PD. In addition to being associated with prevalence of psychosis *GBA* mutations were also associated with a significantly shorter time to psychosis onset (Oeda et al., 2015).

There is evidence that psychosis and dementia have unique mechanisms in PD with one neuropathological study in a cohort with an MMSE > 25 finding only sparse Lewy bodies in the cortex and hippocampus, areas in which Lewy body pathology is greater among cognitively impaired individuals (Kalaitzakis et al., 2009). The question

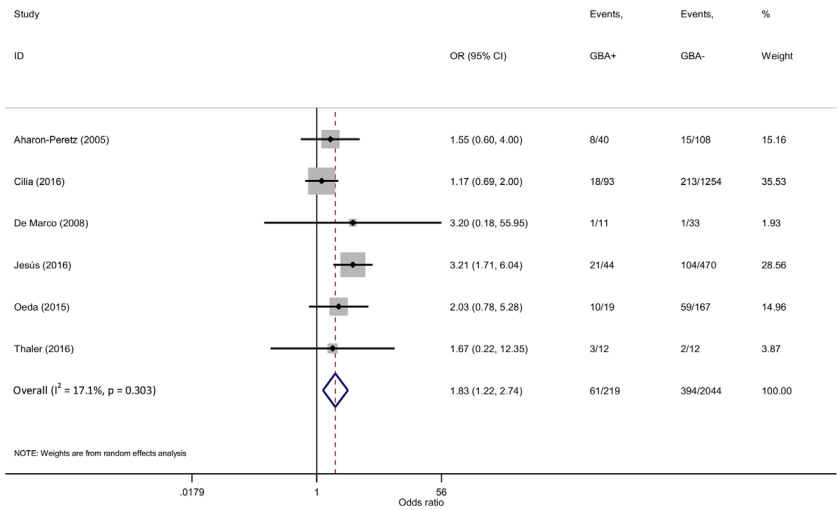

FIGURE 3 Forest plot of psychosis associated with *GBA* mutations. *GBA*+; PD carrying *GBA* mutation; *GBA*−, PD not carrying *GBA* mutations.

of whether the relationship between *GBA* mutations and psychosis is modified by level of cognitive impairment is not possible to conclusively answer on the basis of the studies reviewed here. The stated proportions of cases with significant cognitive impairment in the psychosis studies review here was between 11% and 38% (supplementary Table S3). Overall, there was no clear indication of a relationship between these proportions and the strength of the *GBA* association with psychosis (meta-regression was not possible due to the small number of studies included) but it is worth noting that the only study to specifically exclude individuals with emerging dementia failed to find a significant association. While a small study this finding illustrates the potential value of further analysis in non cognitively impaired *GBA* carriers. Similarly, as shown in supplementary Table S3 there was no apparent relationship between disease duration and direction of association.

The relatively small number of studies assessing the impact of *GBA* on psychosis makes it difficult to analyze the impact of specific mutations. Only Jesús et al. (2016) split E326 K and T369M out from GD-related mutations and found no association with psychosis.

Although there is not unanimity, the evidence on the basis of our meta-analysis and wider review of the literature would suggest a strong relationship between *GBA* mutations and psychosis in PD. However, as with cognition, the mechanisms by which *GBA* mutations give rise to psychosis remain to be established. Hallucinations in PD are associated with cortical, and limbic system Lewy body burden and global cognitive impairment (reviewed in Ffytche et al. (2017)). This neuropathological evidence is consistent with the findings of diffuse cortical and hippocampal Lewy body pathology associated with *GBA* seen in post-mortem and animals models. Moreover, recent neuroimaging data also points to decreased synaptic activity in posterior parietal and occipital areas, also consistent with brain areas implicated in psychosis in PD (Cilia et al., 2016). As described in the cognition section above, Cilia et al. (2016) found that *GBA* cases were more similar to DLB in terms of their neuroimaging profile and on the basis of the clinical phenotype evidence reviewed here it may be the case that psychosis is part of a *GBA* phenotype common across the PD/PDD/DLB spectrum. More work needs to be carried out before this explanation can be conclusively accepted.

2.3 | Depression

Specific inclusion criteria:

- Assessment of depression by standardized assessment tool or evaluation by specialist physician.
- Depression status dichotomized into those with symptoms and those without.

Specific exclusion criteria

- Depression not treated as a binary variable.
- Frequency of depression not reported.

Six studies met the criteria for inclusion into the meta-analysis, resulting in a total patient group of 168 *GBA* mutation carriers and 2,195 non carriers (Brockmann et al., 2011; Jesús et al., 2016; Malec-Litwinowicz et al., 2014; Oeda et al., 2015; Swan et al., 2016; Wang et al., 2014). The Jesús study was treated as described above. A variety of different approaches to coding depression were taken with three studies using a cut off score of ≥14 on the Beck's Depression Inventory (BDI-II), one using a score of >7 on the Hamilton Depression Scale (HDS) and a fifth using a cut off of >16 on the Centre for Epidemiological Studies Depression Scale (CES-D). Depression coding in the remaining two studies was based on clinical interview (supplementary Table S4). One study had a specific exclusion for patients with any psychiatric history but reported levels of depression were broadly in line with the rest of the studies (Malec-Litwinowicz et al., 2014).

GBA mutations were associated with a 2.16-fold increased risk of depression in PD (95%CI: 1.31–3.57; $p = 0.003$, Figure 4), although there was evidence of possible moderate heterogeneity ($I^2 = 40.1\%$; $\chi^2 = 8.34$, df = 5, $p = 0.14$). Moreover the associated funnel plot indicated bias may be present (supplementary Figure S4). In the

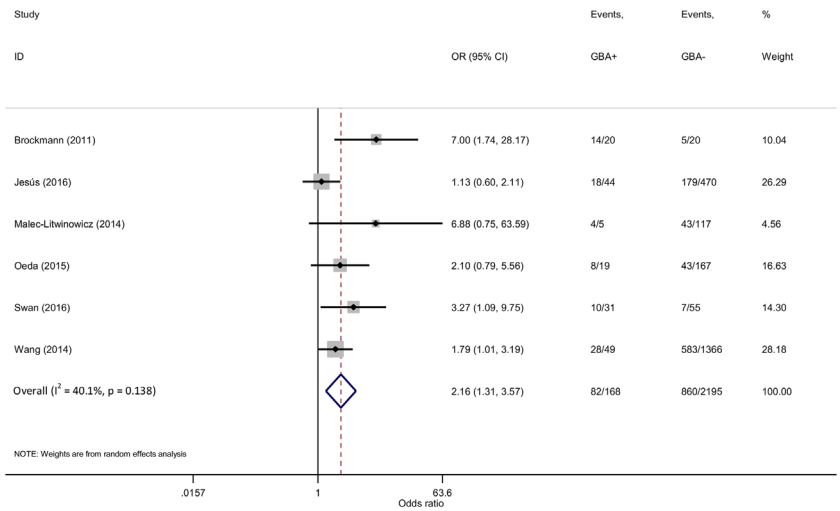

FIGURE 4 Forest plot of depression associated with *GBA* mutations. *GBA*+, PD carrying *GBA* mutation; *GBA*−, PD not carrying GBA mutations.

broader literature, encompassing studies not included in the meta-analysis, mood ratings measured by mean score on the BDI-II, BDI original or by Geriatric Depression Scale were employed by five studies (Alcalay et al., 2012; Brockmann et al., 2011; Swan et al., 2016; Thaler et al., 2016; Winder-Rhodes et al., 2013), four of which failed to find a significant difference (supplementary Table S4). Thus, in light of these findings and the bias indicated by the meta-analysis funnel plot, we would advocate exercising caution before accepting the meta-analysis results. Similarly, to the psychosis literature only Jesús et al. (2016) examined non-GD mutations separately and once again failed to report any significant association.

Evidence has been presented proposing neurobiological alterations associated with *GBA* mutations which are consistent with depressive symptom aetiology. Reduced echogenicity of the brainstem raphe suggestive of dysregulation of the serotonergic system assessed by transcranial sonography was observed by Brockmann et al. (2011). However, there is little other work which specifically points to a mechanistic link between *GBA* mutations and depression and this must also be viewed in light of the wider contradictory literature concerning links between *GBA* mutations and depression in PD.

The discrepancies in findings may be due to depression being a more complex phenotype to identify. Results may be influenced by different alleles of the *GBA* gene coupled with subtle variations in environmental factors such as social support. Heterozygous *GBA* mutation carriers with PD have a higher burden of motor and autonomic symptoms (Pal, Robertson, O'Keefe, & Hall, 2016) which could act as a mediating factor in the apparent association between *GBA* and depression observed here. Equally, it may be the case that *GBA* mutations are associated with severe depression, and the inclusion of more mild phenotypes when measured on numerical scale masks this association. Adding to this difficulty is the lack of congruency of depression assessment scales utilized, fluctuations in the depression phenotype over time and lack of longitudinal data. Moreover, depression and psychosis are likely to have overlapped in many cases in the studies analyzing both of these symptoms, so we cannot be sure that the association with the former is not in part being driven by the latter. Thus, while depression is clearly an important symptom in PD more broadly, it remains unclear whether *GBA* mutations increase risk for it.

2.4 | Other neuropsychiatric symptoms

Although less comprehensively researched, a number of studies have examined the relationship between *GBA* mutations and a broader range of neuropsychiatric symptoms in PD. Anxiety was found to be significantly more common in two studies (Brockmann et al., 2011; Swan et al., 2016) but no relationship was found in two other studies (Jesús et al., 2016; Wang et al., 2014). Thus, in common with depression there is only mixed evidence for anxiety, perhaps for similar reasons. The study by Brockmann et al. (2011) also found higher levels of apathy, sleep disturbance, and eating disorders as measured by Neuropsychiatric Inventory among *GBA* mutation carriers, with no significant difference among other domains providing a further indication of the existence of a broad *GBA*-PD phenotype.

3 | NEUROPSYCHIATRIC PHENOTYPES IN OTHER DISEASES AND HEALTHY ADULTS

3.1 | Dementia with Lewy bodies

GBA mutations are an established risk factor for DLB, underscoring the aetiological similarities between Lewy body spectrum diseases. In one landmark study mutation frequency in DLB was found to be 7.49%, generating an odds ratio of 8 and making the risk for DLB associated with *GBA* mutations higher than that associated with PD (Nalls et al., 2013). In terms of neuropsychiatric phenotypes, here the literature is sparser not least because DLB is underdiagnosed. To our knowledge only one study has examined this relationship. In common with the

established findings in PD this study found that global cognitive impairment, visuospatial dysfunction, and phonemic verbal fluency was greater in *GBA* mutations carriers in an Ashkenazi Jewish population (Shiner et al., 2016). The frequency of hallucinations was also higher (82% in carriers vs. 55% in non carriers) but this did not reach statistical significance ($p = 0.052$) likely to be in part due to the small sample size. Sample size issues in DLB will also be a due to the fact the *GBA* mutations are rare in non Ashkenazi Jewish populations. *GBA* is still under-researched in DLB but these initial findings point to some interesting parallels with neuropsychiatric phenotypes in PD and warrant further investigation in larger cohorts.

3.2 | Gaucher disease

Performance on tasks measuring executive function has been shown to be worse in individuals with Type I Gaucher disease and there is also evidence of impairment in global cognitive function (Biegstraaten et al., 2012; McNeill et al., 2012; Thaler et al., 2016). Interestingly, Thaler et al. (2016) demonstrated a dose effect of *GBA* mutations, with cognitive impairment increasing from PD non carriers, *GBA*-PD to GD-PD. Psychosis is not a central feature of GD, suggesting that the involvement of alpha-synuclein disease processes may be important in the pathogenesis of these symptoms.

3.3 | Healthy adults

It is important to note that not all heterozygous carriers of *GBA* mutations develop PD or DLB, or indeed the phenotypes described above which occur during the disease course. Examination of these individuals may provide important insights into the relationship between *GBA* and the later development of neurodegenerative diseases. The literature in this area is not as extensive as in PD but there is an indication that *GBA* mutations in healthy controls are associated with a degree of cognitive impairment. Given that *GBA* mutations are a strong risk factor for DLB and PD, identifying cognitive changes early on in *GBA* carrying individuals may help to increase the predictive value of the mutation.

A longitudinal study looking at prodromal clinical markers of PD involving regular follow up over 2 years in a cohort of mixed *GBA* heterozygotes with no diagnosis of PD or dementia identified a significant decrease in MMSE and MoCA scores compared to controls (Beavan et al., 2015). The same cohort also showed a significant worsening of depressive symptoms as measured by BDI-II, pointing to the potential utility of these symptoms as an early prognostic indicator in individuals carrying *GBA* mutations in the wider population.

4 | CONCLUSION

Neuropsychiatric symptoms in PD and DLB are common, distressing and challenging to treat. Here, we present further evidence confirming the complex and broad range of symptoms associated with *GBA* mutations in PD. We found strong evidence of association with cognitive impairment and psychosis while the evidence for a relationship with depression was less clear, perhaps because of greater heterogeneity in the aetiology of affective symptoms. Despite this evidence of association, little is known about how the mechanisms underlying the relationship between *GBA* and expression of these neurodegenerative disease phenotypes. On balance the evidence from in vitro, post-mortem, and animal models points to *GBA* mutations driving alpha-synuclein aggregation as a result of either gain of function or loss of function processes. Greater burden of cortical and hippocampal Lewy body pathology seen post-mortem is consistent with the expression of neuropsychiatric phenotypes reviewed here but also indicative of a broader clinical *GBA*-PD phenotype characterized by more severe disease course across a number of neuropsychiatric, motor, and autonomic domains. While the evidence base in DLB is very limited, there is an indication of a similar pattern of association as observed in PD. Moreover, cognitive deficits have been shown in *GBA* mutation carriers without any neurodegeneration. It is not clear why some heterozygous *GBA* mutation carriers remain asymptomatic, nor is it clear what determines whether other carriers develop PD, PDD, or DLB but clearly a complex combination of other genetic and environmental factors plays a part. Further research into symptom progression in PD compared with DLB and studies in controls without neurodegenerative disease, as well as further functional characterization of *GBA* mutations will be important in advancing research in this area.

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