GLUCOCEREBROSIDASE MUTATIONS: A PARADIGM FOR NEURODEGENERATION PATHWAYS

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ABSTRACT

Homozygous glucocerebrosidase gene (*GBA*) mutations cause Gaucher disease, whereas heterozygous mutations are numerically the most important genetic risk factor for Parkinson disease (PD) and are associated with the development of other synucleinopathies, notably Dementia with Lewy Bodies. This phenomenon is not limited to *GBA*, with converging evidence highlighting further examples of autosomal recessive disease genes increasing neurodegeneration risk in heterozygous mutation carriers. Nevertheless, despite extensive research, the cellular mechanisms by which mutations in *GBA*, encoding lysosomal enzyme β-glucocerebrosidase (GCase), predispose to neurodegeneration remain incompletely understood. Alpha-synuclein (A-SYN) accumulation, autophagic lysosomal dysfunction, mitochondrial abnormalities, ER stress and neuroinflammation have been proposed as candidate pathogenic pathways in GBA-linked PD. The observation of GCase and A-SYN interactions in PD initiated the development and evaluation of GCase-targeted therapeutics in PD clinical trials.

KEYWORDS

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Alpha-synuclein
Parkinson Disease
Gaucher Disease
Synucleinopathies
Dementia with Lewy Bodies
Neurodegeneration
Autosomal recessive
Ambroxol

1 Introduction

Recent genetic discoveries have revolutionised our understanding of neurodegenerative diseases (NDDs). Insights provided by the marked acceleration in genetic studies have proven useful in unravelling the complexity of NDD aetiology and pathogenesis. Large-scale genome/whole exome sequencing unveiled a plethora of genetic liability spanning numerous causative genes and NDDs. Newer, unbiased approaches enable the identification of rare gene variants (<1% frequency in the general population), typically missed in genome-wide association studies (GWAS) [1]. Extensive investigations have made it increasingly clear that gene variants play an important role in common, predominantly sporadic NDDs. The establishment of bioinformatics tools and genotype/phenotype databases confirmed genetic factors as key contributors to NDD risk, onset and progression [2].

In the case of Parkinson disease (PD), the identification of causal mutations in over 20 genes and 90 independent risk-associated variants highlighted α-synuclein (A-SYN) aggregation, lysosomal-autophagy and mitochondrial dysfunction as key to PD pathophysiology [3]. In particular, glucocerebrosidase (*GBA*) gene mutations have attracted significant attention amongst the scientific community. Whilst biallelic (homozygous or compound heterozygous) *GBA* mutations are causal for the lysosomal storage disorder (LSD), Gaucher disease (GD), *GBA* mutations constitute the greatest genetic risk factor for the development of PD in either biallelic or heterozygous form [4]. Most studies estimate that 5-15% of PD patients have *GBA* mutations, with this figure increasing to over 30% in the PD Ashkenazi Jewish population [5]. *GBA*-associated PD (*GBA*-PD) is clinically, pathologically and pharmacologically virtually indistinguishable from idiopathic PD (iPD), except for an earlier age of onset and greater cognitive impairment [6]. Studies of families and large population cohorts revealed that heterozygous and biallelic mutations in the *GBA* gene can lead to clinically distinct diseases beyond PD, specifically dementia with Lewy bodies [7, 8]. The molecular mechanisms by which *GBA* mutations increase NDD risk and their pleotropic effects remain largely unknown.

Interestingly, the extensively studied *GBA* gene exemplifies a wider, sui generis principle in neurodegeneration: that carrier status of autosomal recessive (AR) disease, hitherto considered benign, may be associated with an increased risk of a spectrum of NDDs [4, 9-11]. An excessive burden of LSD gene variants in PD and the strikingly distinct allele-dependent clinical phenotypes in patients with *GRN*, *TREM2* and *EIF2AK3* mutations triggered the generalised hypothesis of shared pathophysiological mechanisms between AR disease and NDDs [10-14].

Focusing on *GBA*, this review aims to summarise recent developments on the role of *GBA* in NDDs, particularly in PD. The translation of genetic findings into knowledge of pathogenic mechanisms and *GBA*-targeted therapeutic development will be explored. Accurate characterisation of genetic risk will significantly reform genetic counselling, notably for heterozygous carriers of mutations in *GBA* and other AR disease genes. Indeed, we propose a renewed focussed resurgence of investigations to determine the genetic composition of major NDDs. Insights from the study of gene variants in PD support the notion of aetiological PD

subtypes, likely to exist in other NDDs; testing well-defined patient cohorts may enhance clinical trial efficacy [15]. Pragmatic, intensive and collaborative efforts are thus required to determine key genetic and mechanistic denominators in neurodegeneration which offer to significantly increase therapeutic pipeline development and enable translation of such therapies from laboratory to clinic.

2 *GBA*: Structure and Function

The *GBA* gene contains 11 exons and 10 introns, spanning ~8 kb on chromosome 1q21 [16]. Mapped to a very gene-rich area, 9 genes and 2 highly homologous pseudogenes, *GBAP1* and *MTX1P*, are found within 100 kb of sequence. Both pseudogenes appear to have resulted from a duplication event ~36-48 million years ago [17]. *GBAP1* shares 96% exonic sequence identity with *GBA*, reaching up to 98% between intron 8 and the 3' untranslated region. A 55-bp deletion in exon 9 and missing intronic *Alu* sequences distinguishes *GBAP1* from the functional *GBA* gene [16]. The high homology and proximity between *GBA* and its pseudogenes enable reciprocal and non-reciprocal homologous recombination events, forming complex alleles by gene duplication, conversion or fusion [18]. *GBA* analysis is complicated by these nearby pseudogenes [19, 20]; alternative strategies to overcome such issues include Illumina targeted sequencing protocols and long-read sequencers [21-23].

β-glucocerebrosidase (GCase), encoded by the *GBA* gene, is a 497-amino acid (AA) lysosomal hydrolase that metabolises glucosylceramide (GlcCer) into glucose and ceramide. *GBA* transcription is regulated by transcription factor EB (TFEB), the master regulator of the CLEAR (coordinated lysosomal expression and regulation) pathway involved in lysosomal biogenesis. GCase is then synthesised, truncated and glycosylated in the endoplasmic reticulum (ER). Due to two in-frame ATG translational start sites, GCase is transcribed as a 536 or 516 AA protein and processed into the functional 497 AA enzyme while entering the ER [18]. Following post-translational modifications, a GCase-LIMP2 complex is trafficked through the trans-Golgi network and GCase localises with the lysosomal membrane following a pH-dependent dissociation from LIMP2. Once in the lysosome, an interaction between GCase and the activator protein, Saposin C, is required for its proper function [24].

A comprehensive structural review of GCase has been reported in the literature [25, 26]. The X-ray structure of GCase was first described in 2003 [27]. X-ray studies have shown that GCase has three tertiary structure domains: domain I (residues 1–27 and 383–414) comprising an anti-parallel β-sheet flanked by a loop and two disulphide bridges; domain II (residues 30–75 and 431–497), an 8-stranded β-barrel resembling an immunoglobulin-like fold, and domain III (residues 76–381 and 416–430) is a $(\beta/\alpha)_8$ triosephosphate isomerase (TIM) barrel containing the active site of the protein [27]. The active site is a catalytic dyad, consisting of the nucleophile residue Glu 340 and acid-base residue Glu 235, and capped by three loops (residues 312-319, 341-350, and 393-396) [27]. Adopting multiple pH-dependent conformations, these loops provide structural flexibility and confer GCase a higher affinity for its substrates [28]. In addition, the mature human GCase

protein has five potential Asn residues, with the first four normally occupied (Asn 19, Asn 59, Asn 146, Asn 270 and Asn 462) [29]. N-glycosylation is essential for the development of a catalytically active enzyme, especially at Asn 19 [29]. The Asn19-linked glycan confers conformational stability, flanking the enzyme catalytic dyad and residues 438-445, where the common and severe mutation (L444P) is found [30]. Targeting the glycosylation pathway may be a potential therapeutic strategy; the conformational effects of modulating GCase glycosylation in mutants remains to be elucidated.

3 *GBA* Mutations and Gaucher Disease

Biallelic *GBA* mutations are pathognomonic for Gaucher disease (GD), an LSD characterised by GlcCer-laden macrophages in the bone marrow, spleen and liver, known as Gaucher cells [31]. Systemic features include hepatosplenomegaly, pancytopenia, bone involvement and neurological deficits [32]. Data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry (clinicaltrials.gov NCT00358943) enabled the delineation of the GD phenotypic spectrum. Typical GD classifications comprised 3 broad phenotypes, non-neuronopathic (type 1, the most common form) and neuronopathic (acute, type 2 and chronic, type 3), based on clinical progression, life expectancy and neurological involvement [33]. Neurological symptom onset in type 2, the most severe form of GD, is before 6 months of age leading to death within 2 years of life [34]. Type 3 GD has a slower disease progression and patients typically live into adulthood [34]. Neurological manifestations include myoclonic or generalised seizures, extrapyramidal features, supranuclear ophthalmoplegia, oculomotor apraxia and developmental delays [34]. Nevertheless, following the range of presentations observed, the notion of a spectrum of GD phenotypes, with varying degrees of severity, is now widely accepted [35].

To date, over 495 disease-causing *GBA* mutations, encompassing insertions, deletions, point mutations, frameshifts and recombinant alleles, have been described (The Human Gene Mutation Database, http://www.hgmd.org) [4, 18]. Among the Ashkenazi Jewish (AJ) population, a significantly higher burden of *GBA* mutations is observed (one in 14-18) compared to a carrier frequency of just <1% in other ethnic groups [4]. Indeed, four specific *GBA* mutations (N370S, L444P, 84GG and IVS2+1G>A) account for ~90% of disease alleles among the AJ population (Figure 1) [36, 37]. Moreover, recombination events between intron 2 and exon 11 compose a key class of *GBA* mutants; over 20 recombinant alleles have been reported, with RecNil and RecΔ55 being the most frequent [18]. RecNil incorporates missense mutations L444P, A456P and V460V derived as a result of a non-homologous cross-over junction area between intron 9 and exon 10 of *GBA* and pseudogene *GBAP1* [18]. The aforementioned 55-bp deletion in *GBA* exon 9 and corresponding deleted section of *GBAP1* constitutes RecΔ55 [38].

Ethnicity and GD phenotype contribute significantly to the distribution of *GBA* mutations. The N370S *GBA* mutation accounts for 70% of mutant alleles in AJ patients [37]. Of note, Iberians demonstrate a greater frequency of N370S *GBA* alleles (Portuguese: 63%; Spanish: 46%) than

non-Jewish European GD patients [39, 40]. Such findings clearly illustrate the contribution of both Ashkenazi and Sephardi Jewish ancestry to the modern Iberian population. The N370S *GBA* allele is seldom observed in Chinese, Japanese, Thai and Korean cohorts [18, 41]. Indeed, L444P, F252I and RecNil *GBA* alleles, associated with neuronopathic GD types 2 and 3, are more prevalent in Asian populations [42-44]. Further, specific *GBA* mutations may be predictive of GD phenotype. Biallelic N370S *GBA* mutations are synonymous with mild GD type 1, although some subjects remain asymptomatic for the disease, not reaching medical attention [18]. Severe *GBA* mutation L444P, located at the interface of the TIM barrel, accounts for >40% of mutations in analyses of neuropathic Type 2 and 3 GD patients [45, 46]. Although phenotypic predictions may be tentatively conducted based on genotype, the genotype-phenotype correlation remains incomplete. Divergent phenotypes in family members harbouring identical *GBA* mutations has implicated the role of disease modifiers [47].

Adding further complexity is the interesting E326K *GBA* substitution mutation. Located in domain III, E326K is the most prevalent PD-associated *GBA* mutation yet does not cause GD in a homozygous state [48]. Interestingly, only a subtle concomitant reduction in GCase activity has been reported in E326K *GBA* homozygotes, perhaps explaining its non-GD pathogenicity [49]. The association between T369M *GBA* variant and PD is also under investigation following reports homozygotes do not develop clinical features of GD [48].

4 The Link Between *GBA* and Parkinson Disease

4.1 *GBA* and PD: Genetic Risk

Recognition of the GD-PD association began in the 1990s following initial case reports of typical, progressive parkinsonian features amongst a subset of GD type 1 patients [50-52], challenging the classical paradigm denoting type 1 GD as non-neuronopathic. Further observations that obligate and confirmed *GBA* carriers also exhibit increased rates of PD prompted a more comprehensive review [53]. A landmark international multicentre genetic analysis provided definitive confirmation of this genetic association, noting a higher prevalence of *GBA* mutations among 5691 PD patients compared to 4898 controls with an estimated odds ratio of 5.43 [4]. Of note, there is no significant difference in PD risk between heterozygous and biallelic *GBA* mutation carriers [54]. Follow-up GWAS and over 50 population studies across diverse cohorts have replicated these findings [55-57], reaffirming *GBA* mutations as numerically the greatest genetic PD risk factor.

Present in approximately 5-15% of PD patients, *GBA* mutations are estimated to confer a cumulative 10-30% risk of developing PD by age 80, a 20-30-fold increase compared to non-carriers [4, 54]. Analogous to GD, genotyping studies in 2009 have revealed that N370S and L444P *GBA* mutations are most prevalent, accounting for ~50% of all *GBA*-associated PD (*GBA*-PD) cases [4]. The E326K GBA mutation, albeit absent in the GD population, is now thought to be the most significant PD-associated *GBA* mutation [48]. An increased PD risk was only observed in the

context of specific ancestry: *GBA* variants R496H and 84GG for AJ patients; R120W for East Asian subjects and N370S, E326K, D409H and H225Q in European or West Asian populations [57]. PD risk can also be stratified according to genotype: meta-analyses report that severe (84GG, V394L, D409H, L444P) and mild (N370S, R496H) *GBA* mutations increased the PD development risk by 13.6- and 2.2-fold, respectively [58]. Further, new PD-associated *GBA* variants are being continuously discovered, such as W378R in Australian families [59] and L216I in Chinese populations [60]; the effect on PD risk of new *GBA* variants is yet to be ascertained. A recent large study investigated the suggestion that certain GBA haplotypes may be associated with earlier age of onset of PD, but found no such effect (Toffoli et al Mov. Dis. 2021).

4.2 *GBA*-PD Clinical Features

GBA-PD is clinically, pathologically and pharmacologically virtually indistinguishable from iPD [6]. *GBA*-PD patients exhibit the classic triad of tremor, rigidity and bradykinesia, with typical neuropathological iPD hallmarks of brainstem and cortical Lewy Bodies [5]. Distinct characteristics include: an earlier age-of-onset (3-6 years and 6-11 years earlier in heterozygous and biallelic *GBA* mutation carriers, respectively); greater motor and cognitive decline; quicker progression to advanced PD therapies (deep brain stimulation, continuous apomorphine, intestinal levodopa) and earlier death [61-64]. A comprehensive review of *GBA*-PD cohorts is found in the literature [65]. Non-motor symptoms, REM sleep behaviour disorder (RBD), depression, anxiety, visual hallucinations and autonomic dysfunction, are more common among *GBA*-PD patients compared to iPD [66-68]. Increased incidence of dysautonomic features has been proposed as the key driver of reduced survival rates amongst this patient cohort [62]. Further, motor complications, such as gait freezing, dysarthria and dysphagia are more prevalent in *GBA*-PD patients. Sex is an important factor for the development of PD; it remains to be determined whether sex differences observed in iPD centring on age of onset [69], disease presentation [70, 71] and biochemical markers [72] are retained in *GBA*-PD cohorts. A ‘dose effect’, whereby biallelic *GBA* mutation carriers typically present with greater PD severity than their than heterozygous counterparts, is recognised [68, 73]. Profound phenotypic modifications attributed to specific *GBA* mutations have also been observed: carrier status of severe *GBA* mutations confer an earlier age of PD onset (average by 5 years), a 2- to 3-fold increased dementia risk and rapid progression of non-motor symptoms compared to mild mutation carriers [61, 68, 74]. Mechanisms underlying the differential effects of specific *GBA* mutations on age-of-onset and PD risk/severity as yet remain elusive; hypotheses postulate that different conformational changes dependent on mutation location may modify PD phenotype.

Neuroimaging of *GBA*-PD closely resembles iPD patients. Key differences may enable the use of neuroimaging as an early diagnostic indicator and method for tracking PD progression. Functional brain imaging consistently reports significant reduction in cortical parietooccipital resting activity in *GBA*-PD compared to iPD patients, particularly more pronounced in carriers of severe *GBA* mutation than mild [61, 75-77]. Such cortical dysfunction is a pathological DLB hallmark, likely

observed in the *GBA*-PD cohort due to greater Lewy body pathology [78]. Indeed, parietooccipital dysfunction may provide an explanation for the higher prevalence of visual hallucinations in *GBA*-PD patients [79]. Analyses of nigrostriatal function revealed reduced but comparable activity levels in dopaminergic presynaptic terminals in *GBA*-PD patients compared to iPD, displaying greater striatal asymmetry index differentially affected by mutation severity [76]. Contrastingly, transcranial sonography showed greater echogenicity in *GBA*-PD patients independent of mutation severity and reduced echogenicity of brainstem raphe nuclei as seen in iPD [80]. Of interest, biallelic and heterozygous *GBA* mutation carriers without PD display increased nigral ^{11}C-(R)-PK11195 BP_{ND} binding potential, a PET imaging marker detecting neuroinflammation [81]. However, it is important to acknowledge that such differences remain subtle and largely confined to research purposes at present.

5 GBA mutations in other synucleinopathies

Studies of *GBA* have been extended to other synucleinopathies, including dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Inclusions of fibrillated A-SYN within brainstem or cortical regions are characteristic of such disorders. In DLB, *GBA* mutations were detected in 7.49% of cases (odds ratio of 8.28), increasing to 31% in AJ cohorts, suggesting that *GBA* may be a stronger risk factor for DLB than PD [82, 83]. GWAS studies confirmed that *GBA* mutations, particularly the rs35749011 variant, was significantly associated with DLB [84, 85]. Interestingly, a relative 3-fold increased risk of developing DLB compared to PD was noted among *GBA* carriers [86]. In DLB, *GBA* mutations are associated with earlier disease onset (~5 years) and are more prevalent in men [87]. A more aggressive disease course, including a greater severity of cognitive dysfunction, RBD and motor decline, has been observed in DLB patients carrying *GBA* mutations compared to non-carriers [83]. Reduced GCase activity and significant alterations in lipid profiles are observed in the brains of DLB *GBA* mutation carriers [88]. Rare and frequently pathogenic *GBA* variants have been detected in DLB patients, including N370S, L444P and E326K [82, 83, 87, 89]. Further studies are required to ascertain the link between disease risk/phenotype and type of *GBA* variant.

Studies of *GBA* in MSA have been limited by disease rarity, lack of neuropathological confirmation of MSA and incomplete genetic analyses of *GBA*. Partial evidence supports the link between *GBA* and MSA. Sequencing *GBA* coding regions and flanking splice sites in 969 MSA patients and 1509 controls demonstrated a combined carrier frequency of 1.75% across Japanese, European and North American cohorts (0.73% in controls) [7]. *GBA* N370S, T369M and R496H mutations, were more prevalent in autopsy-confirmed MSA cases (23.5%) compared to Alzheimer disease (AD) cases (3.7%) [90]. A recent investigation of rare variant burden across 54 LSD genes in 375 MSA patients and 587 controls failed to replicate an association between *GBA* and MSA [91], with others reaffirming such findings [92-94]. A-SYN deposition occurs in oligodendroglial

cytoplasmic inclusions in MSA, as opposed to the classic intraneuronal inclusions observed in PD and DLB [95], a distinction which may underlie key differences in disease pathogenesis.

RBD is a prodromal condition for synucleinopathies, PD, DLB and MSA. With RBD patients displaying phenoconversion rates of 80% and latencies of up to 15 years prior to symptom onset, RBD is a marker for synucleinopathy development [96]. A higher frequency of RBD is observed in *GBA*-PD compared to iPD [68]. PD patients with concomitant GD have a higher risk of developing RBD than their heterozygous counterparts and iPD (33%, 24%, 18.6%, respectively) [68]. Further, *GBA* mutations are associated with idiopathic RBD [97-99]. *GBA* mutation carriers present with significantly worse RBD scores than non-carriers [100]. RBD-associated PD and *GBA*-PD patients may have greater spread of A-SYN pathology compared to iPD [101, 102]. It remains unclear whether *GBA* mutations affect rate of phenoconversion to parkinsonism, with findings largely inconsistent [98, 103].

6 Proposed Mechanisms for GBA-associated parkinsonism

It has been more than 15 years since the link between PD development and carrier status of *GBA* mutations was initially acknowledged. However, it remains unclear how *GBA* mutations predispose to parkinsonism [104]. Extensive GD and PD registries provide a wealth of shared data and biorepositories, facilitating large-scale investigations into the putative pathogenic mechanisms of *GBA* mutations. Indeed, the majority of such work focusses on PD development, with disease rarity of other NDDs hindering explorations. Importantly, emerging candidate pathways include A-SYN accumulation, autophagic lysosomal dysfunction, mitochondrial abnormalities, ER stress and neuroinflammation, which will be further discussed [65].

6.1 GCase and Alpha-Synuclein

Given the observed non-Mendelian inheritance of *GBA*-PD, loss- or gain-of-function and a bidirectional positive feedback loop are all proposed mechanisms behind its pathogenesis [65]. Each model has inherent limitations with experimental findings contesting their mutual exclusivity; multiple mechanisms may be in place. Figure 2 demonstrates an overview of the contribution of GCase dysfunction to the PD pathogenesis.

According to the loss-of-function hypothesis, *GBA* mutations may affect GCase protein structure, invariably leading to reduced GCase activity, the degree of which is mutation dependent [5]. No clinical correlation between *GBA* mutations, level of GCase activity and GD/PD phenotype has been observed; possible structural consequences of mutations preventing GCase exerting its function within the lysosome may play a significant role [105]. Indeed, GCase loss of function may occur via multiple mechanisms, including: (1) ER GCase retention, (2) impaired transportation of GCase from Golgi to lysosome via its *SCARB2*-encoded transporter, LIMP2, (3) unfolded protein response (UPR)-associated degradation, (4) active site mutations and defects in activator protein, Saposin C. GD patients carrying severe *GBA* mutations (L444P, D409H, P415R) demonstrate a

greater degree of ER GCase retention and ER-associated degradation via proteasomes than mild mutations carriers [106]. GCase may have an intrinsic role in PD pathogenesis; detailed biochemical analyses of both *GBA*-PD and iPD cohorts identified a reduction in GCase activity in blood [107], fibroblasts [108], cerebrospinal fluid (CSF) [109] and brain tissue, most pronounced in the substantia nigra [110-112]. GCase deficiency leads to cytotoxic substrate GlcCer, glucosylsphingosine (GlcSph) and galactosylceramide (GalCer) accumulation, ensuing in lipid dyshomeostasis [113, 114]. Excess GCase substrates in cultured neurones saturates A-SYN trafficking, processing and clearance pathways [115, 116]. GlcCer may also directly induce amyloid A-SYN formation, stabilising oligomeric intermediates [116]. In vitro and in vivo work revealed that GlcSph accumulates before GlcCer, and GlcSph and other GlcCer downstream metabolites enhance A-SYN seeding [117]. Moreover, A-SYN aggregation is observed in many LSDs characterised by lipid dyshomeostasis [118, 119], suggesting lipid rafts may have an essential role in A-SYN synaptic localisation [120]. Indeed, an excessive burden of genes involved in ceramide metabolism are now known to be associated with PD pathogenesis, providing support to this hypothesis [10]. Rocha et al. [121] observed a concomitant increase in GlcSph levels with reduced GCase activity in the substantia nigra and hippocampi of iPD brains. GCase inhibition via *GBA* knockout and conduritol-β-epoxide (CBE) treatment in various cell and animal models leads to lipid and A-SYN accumulation [122-126]. Huebecker et al. [127] showed an increase in GlcCer levels in the substantia nigra of iPD brains, conflicting with prior investigations in other iPD and *GBA*-PD cohorts [110, 128]. Such discrepancies underlie the debate over the therapeutic potential of GlcCer synthase inhibitors in PD; the development of one GlcCer synthase inhibitor, venglustat (GZ/SAR402671), was halted in early 2021 after it failed to meet its Phase II primary endpoint of improving PD motor function. Limitations of the loss-of-function model include: (1) a minority of GD patients, despite negligible GCase activity, develop PD and (2) *GBA* E326K mutation, whilst not associated with a significant reduction in GCase activity, is the most prevalent PD-associated *GBA* mutation, implying that reduced GCase activity is unlikely to be the sole cause of the observed A-SYN accumulation in *GBA*-PD [48, 129].

Most *GBA* mutations are missense, leading to misfolded protein. Mutant GCase may be retained in the ER activating UPR and ER-associated protein degradation (ERAD). The gain-of-function hypothesis proposes that such cellular dysfunction and altered GCase/A-SYN interactions work to promote A-SYN accumulation and aggregation [130]. Immunofluorescence studies on brain samples from *GBA*-PD patients confirmed co-localisation of mutant GCase and A-SYN in 32-90% of Lewy Bodies and neurites [131]. Over-expression of mutant GCase (containing N370S, L444P, D409H, D409V, E235A, and E340A) significantly raised A-SYN levels in neural MES23.5 and PC12 cells [132], a finding replicated in several cerebral regions of mice carrying the homozygous V394L and D409H *GBA* mutations [133, 134]. Mutant GCase may contribute to lysosomal dysfunction by impairing autophagy or saturating the ubiquitin-proteasome

pathway (UPS). This mechanism is challenged by null mutations (84GG, IVS2+1, R359X), which do not encode the GCase protein, but are indeed associated with PD [58, 135].

Another, third hypothesis proposes a self-propagating bidirectional feedback loop in which GCase deficiency promotes A-SYN oligomerisation, leading to even greater depletion of lysosomal GCase and further stabilisation of A-SYN oligomers by GlcCer accumulation [116]. Overexpression of A-SYN in SH-SY5Y cells led to reduced GCase activity and protein levels [112]. GCase activation via small molecule therapy and adeno-associated virus-mediated *GBA* expression in in vitro models ameliorated A-SYN aggregation, lysosomal dysfunction and phenotypic deficits [136, 137]. In vivo work reports no such correlation between total A-SYN levels and GCase activity [138-140]. Henderson et al. [139] proposed that GCase activity modulates neuronal susceptibility to A-SYN pathology, an effect driven by extent of A-SYN seeding. Indeed, given that only a small proportion of carriers of *GBA* mutations undergo PD phenoconversion, it is likely other factors must be at play.

6.2 GCase and the Autophagy-Lysosomal Pathway

Autophagy refers to the lysosomal pathway by which intracellular components are degraded. Chaperone-mediated autophagy (CMA) involves the selective targeting of pentapeptide motif KFERQ-containing proteins delivered to lysosomes via chaperone hsc70 and translocated by integral membrane protein LAMP2A [141]. Bulk degradation of larger cytoplasmic proteins by forming double-layered autophagosomes is termed macroautophagy [141]. A-SYN clearance is mediated by both CMA and macroautophagy [142].

GCase deficiency and resultant substrate accumulation reduce lysosomal degradation capacity, impairing autophagy [143]. Indeed, autophagy-lysosomal pathway (ALP) deficits are central to *GBA*-PD, and iPD, pathogenesis [144-147]. *GBA*-N370S induced pluripotent stem cell (iPSCs)-derived dopamine neurones display an increase in macroautophagy markers p62 and LC3II, enlarged lysosomes and reduced autophagic flux [147]. Notably, Magalhaes et al. [143] found that GCase deficient cells exhibit altered lysosomal biogenesis. ALP dysfunction may enhance cell-to-cell A-SYN propagation [146] by increased exosomal A-SYN release [148, 149], perhaps accounting for the accelerated clinical course observed in *GBA*-PD. Moreover, pathologic A-SYN forms high-affinity bonds with LAMP2A, competitively inhibiting CMA [142, 150]. With investigations into the role of ALP dysfunction in PD pathophysiology centred on in vitro models, further work is required to clarify this association.

6.3 GCase, Mitochondrial dysfunction, ER stress and Neuroinflammation

Mitochondrial dysfunction has been classically involved in iPD [151], with suggestions it may also feature in *GBA*-PD [122]. CBE inhibition in SHSY-5Y neuroblastoma cells resulted in decreased mitochondrial membrane potential (ψm), mitochondrial fragmentation and excess

free radical generation [122]. Reductions in ψm and oxygen consumption were reported in GD fibroblasts and GD mouse models [123, 152]. Of note, levels of electron transport chain carrier coenzyme Q_{10} and ATP decreased by 24% and 30%, respectively, in these fibroblasts [152]. Altered mitochondrial morphology has been reported in a GD mouse model, noting lost cristae organisation and electron dense mitochondria [134]. Li et al. [153] examined the link between heterozygous *GBA* mutation and mitochondrial dysfunction, with $GBA^{L444P/WT}$ mice exhibiting inhibition of mitochondrial priming and autophagy, mirroring findings of post-mortem *GBA*-PD patient studies. This disruption renders cells more susceptible to oxidative stress, increasing A-SYN accumulation through both *GBA* gain- and loss-of-function mechanisms. Moreover, NAD+ supplementation with NAD+ precursor, nicotinamide riboside, prevents age-related loss of dopaminergic neurones and motor decline in *GBA*-PD *Drosophila* model [154]. *Drosophila* do not have a homologue of A-SYN thus, such pathology is notably A-SYN-independent. The cause for mitochondrial dysfunction in GCase deficiency is unclear but likely secondary to the aforementioned ALP dysfunction, lipid dyshomeostasis, calcium dysregulation, ER stress and neuroinflammation [155].

GCase-mediated ER stress and UPR activation may contribute to the development of parkinsonism. Mutant misfolded GCase is retained in the ER, triggering ER stress and evokes parkin-mediated proteasomal degradation of GCase [156]. Correlations between ER retention of GCase and GD severity have been observed [106]. Further, upregulation of UPR mediators, namely BiP, calreticulin, PDI, calnexin and IRE1α has been noted in human *GBA*-N370S PD iPSC-derived dopamine neurones compared to controls [147]. In particular, Gegg et al. [112] reported a 63% increase in transcription of C/EBP homologous protein and 26% increase in BiP levels in the putamen of *GBA*-PD brains. Removal of A-SYN aggregates may be achieved with early intervention to reduce ER stress, a potentially valuable therapeutic approach [157].

Neuroinflammation has long been associated with PD [158]. *GBA* knockout animals and CBE-treated mice provide evidence of significant microglial activation preceding neuronal cell death [125, 159-161]. Mullin et al. [81] reported that biallelic and heterozygous *GBA* mutation carriers without PD display increased nigral ^{11}C-(R)-PK11195 BP_{ND} binding potential, a PET imaging marker detecting neuroinflammation. ALP dysfunction in GCase deficient glia may exacerbate the spread of A-SYN pathology [162]. It remains unclear whether microglial activation is indeed a cytotoxic or neuroprotective process [81].

7 Clinical Implications of *GBA* Mutations

GBA represents a focal point for the search of biomarkers and development of disease-modifying therapies, with investigations converging on PD. Despite intensive efforts, the vast evidence base regarding *GBA*-PD is yet to impact patient care. Genetic testing remains largely reserved for

research purposes, with only a minority of PD patients familiar with the *GBA* gene [163]. With the advent of precision medicine, it is hoped that improved genetic stratification of large, heterogenous PD patient cohorts may highlight predictive, diagnostic and prognostic biomarkers [15]. GCase-targeted therapeutics may also be beneficial in iPD, where a GCase deficiency has been described in blood [107], CSF [164] and brain tissue [112]. Further exploration is required to ascertain the clinical value of *GBA* mutations in DLB, MSA and wider field of neurodegeneration.

7.1 GCase-Targeted Biomarkers

A critical need exists to develop reliable biomarkers in neurodegeneration, particularly in PD where there is a significant lag between onset of neuropathological changes and motor symptoms [165]. Up to 60% of dopaminergic neurones in the substantia nigra pars compacta have undergone cell death prior to PD diagnosis [165]. To date, the search for robust biomarkers has yielded negative and inconclusive results, hindered by disease heterogeneity [15]. *GBA*-PD patients represent a unique, more homogenous cohort enabling accurate characterisation of potential biomarkers, with GCase-targeted biomarkers the focus of such investigations.

Driven by technological advances and sample accessibility, identifying biospecimen-based (blood, CSF, saliva, urine or biopsy) PD biomarkers has overtaken traditional neuroimaging and electrophysiological investigations as a research focal point [166]. In most biospecimens, GCase activity is generally lower in PD, regardless of *GBA* mutation status. A reduction of GCase activity has been reported in fibroblasts and CSF from *GBA*-PD and iPD patients [167-169]. Stratifying patients according to Hoehn and Yahr (H&Y) scores revealed significantly reduced GCase in early stages of the disease [164]. Biomarker combinations of CSF GCase, oligomeric/total A-SYN ratio and age achieved 82% sensitivity and 71% specificity in distinguishing PD from healthy controls [164]. Prior literature supports a decrease in GCase activity in dried blood spots from both *GBA*-PD and iPD [107], particularly in monocytes [170]. Alcalay et al. [107] suggested that the observed levels of GCase activity may not be pathogenic for PD and thus not a reliable biomarker, proposing its evaluation as an alternative measure of therapeutic target engagement. Others have reported no differences in GCase activity between iPD and healthy subjects [171-173], albeit higher GCase activity was associated with longer disease duration in iPD [107, 174].

Alternative methods to assess GCase activity include the characterisation of intermediates, products and related lysosomal enzymes involved in its metabolic pathways. Deranged fatty acid metabolism has been observed in *GBA*-PD, notably lower levels of CSF omega-3 and omega-6 [175], and increased plasma hexosylsphingosine levels compared with iPD and controls [176]. iPD patients display higher levels of plasma ceramide and monohexosylceramide, positively correlating with cognitive impairment [177]. Alterations in lysosomal hydrolases may also serve as a broader NDD marker. Studies of human post-mortem substantia nigra of iPD cohorts revealed deficiencies in α-galactosidase, β-hexosaminidase, GCase, *GBA2*, in addition to, glycosphingolipid substrate accumulation [127]. RBD patients display reductions in serum gangliosides [127]. Moreover, CSF alpha-mannosidase activity showed a marked decrease in AD, DLB and fronto-temporal dementia

(FTD) patients, with a selective loss in CSF GCase activity noted in DLB versus controls [178]. It is notable that differences in CSF sample collection/storage procedures and intrinsic instability of lysosomal enzymes may impede comparisons between studies [179].

7.2 GCase-Targeted Therapies

There is no current effective disease-modifying therapy for PD. Given the proposed significance of GCase deficiency to PD etiology, GCase modulation represents a potential therapeutic avenue. Successful systemic GD treatments, enzyme replacement therapy (i.e., imiglucerase (Cerezyme), Taliglucerase alfa (Elelyso) and Velaglucerase alfa (VPRIV)), cannot cross the blood brain barrier, proving ineffective in alleviating neurological symptoms. GCase-targeted experimental strategies in clinical trials for PD are founded on the reciprocal relationship between GCase deficiency and A-SYN deposition, aiming to (1) restore GCase enzymatic function via small-molecule chaperones (SMCs) and gene therapy, or (2) modulate sphingolipid turnover with glucosylceramide synthase inhibitors (Table 1) [166, 180].

SMCs stabilise and refold misfolded GCase protein, upregulating post-ER translocation of mutant GCase to the lysosome and thus, increasing its catalytic activity. This therapeutic approach will not only reduce ER stress, but also improve lysosomal function and A-SYN degradation [181]. Two types of SMCs exist, inhibitory (which binds to the GCase active site, antagonising the binding of substrates until low lysosomal pH results in dissociation) and non-inhibitory chaperones (binds to alternate parts of GCase, modulating post-translational folding). Drug screens have discovered several novel SMCs, the majority being inhibitory [182, 183]. Ambroxol is one of the most promising candidates as a disease-modifying therapy for PD and related synucleinopathies. As a repurposed mucolytic, ambroxol has an excellent safety profile. Administration of ambroxol reversed the effects of *GBA* mutations in GD mouse models, *Drosophila* expressing N370S and L444P *GBA* and patient-derived fibroblasts [108, 184, 185]. Neural crest stem cell-derived dopaminergic neurones demonstrated that ambroxol therapy increased GCase protein levels/activity, reduced A-SYN accumulation and rescued autophagic defects [186]. A-SYN levels were also reduced by ambroxol in transgenic *A-SYN/A-SYN* mice [187]. Phase II clinical trials are evaluating the safety, tolerability and pharmacodynamics of ambroxol in PD (NCT02941822, AiM-PD trial) and PD dementia patients (NCT02914366). The AiM-PD study confirmed ambroxol therapy to be safe and well tolerated, with sufficient levels of CSF penetration and target engagement achieved [188]. A significant increase in CSF A-SYN concentration (13%) and GCase protein (35%) was reported. There was also an improvement in PD motor symptom severity, although being an open label study this effect is most likely attributable to a placebo effect. Nevertheless, this observation confirms that ambroxol at least does not interfere with the effectiveness of dopaminergic therapy [188]. Extracellular export of A-SYN from brain parenchyma may account for the increase in CSF A-SYN observed. Notably, two further clinical trials to assess safety, tolerability and the effect of ambroxol on cognition, functional decline and neuropsychiatric symptoms in DLB patients are due

to commence (NCT04405596 and NCT04588285). Another approach that is being tested by Lysosomal Therapeutics Inc. is LTI-291, a non-inhibitory SMC (Netherlands Trial Register: NTR6960 and NTR7299). Published data from first-in-human studies noted LTI-291 was well tolerated with no sudden adverse events in healthy volunteers, supporting the continued exploration of LTI-291 effects in the *GBA*-PD population [189].

Gene therapy as a means to enhance GCase activity holds great promise, currently in trials for several LSDs (NCT02716246, NCT03315182) and Spinal Muscular Atrophy (NCT03505099). The use of adeno-associated viral vectors (AAVs) to insert wild-type *GBA* alleles into the genome of *GBA* mutation carriers is under investigation. AAV-mediated *GBA* delivery in mice resulted in increased GCase activity, reduced A-SYN and aberrant lipid accumulation, together with improved cognitive deficits [190, 191]. Co-injection of AAV-*GBA* with AAV-A53T *A-SYN* in rats prevented degeneration of nigrostriatal dopaminergic neurones [191]. Intravenous delivery of (AAV)-PHP.B-*GBA* in mice restored physiological GCase levels and led to almost complete clearance of A-SYN deposits [192]. Systemic AAV delivery is advantageous, notably being able to treat non-selective areas of the brain. A prolongation of life span, rescued neurodegeneration and ameliorated motor deficits was observed following systemic AAV9-*GBA* delivery in GD mouse models [193]. *GBA*-targeted gene therapy via intracisternal AAV9 vector (PR001A) administration is under evaluation in *GBA*-PD patients (PROPEL trial, NCT04127578) and infants with Type 2 GD (PROVIDE trial, NCT04411654). Estimated completion date for both Phase I/II trials is 2027 and 2028, respectively.

Substrate reduction therapy (SRT) inhibits the aberrant GlcCer accumulation observed in GCase deficiency and is approved for the treatment of GD. Investigators have sought to determine its potential use in *GBA*-PD. GlcCer synthase inhibitor, GZ667161, reduced GlcCer and GlcSph levels in GD mouse models, halting the accumulation of hippocampal aggregates of ubiquitin, tau and A-SYN, and significantly improving behavioural alterations [194]. Based on these findings, the safety, tolerability and efficacy of GlcCer synthase inhibitor, venglustat (GZ/SAR402671, analogue to GZ667161), was tested in the randomised, placebo-controlled, double-blind MOVES-PD trial (NCT02906020). Despite a favourable safety and tolerability profile, although was associated with early onset worsening of motor function [195]; the trial failed to meet its primary endpoint of improved motor function after 12 months, and development of venglustat subsequently halted in 2021. Concerns exist over SRT efficacy as a PD therapy given that whether substrate accumulation occurs in the brains of GBA-PD patients remains a subject of controversy [128].

Glucocerebrosidase (*GBA*) Mutations: A Paradigm for Neurodegeneration

TABLE 1 GCase-Targeted Therapies in PD Clinical Trials

Compound	**Mechanism of Action**	**Target enrolling population (n)**	**Primary Outcomes**	**Placebo**	**Status**	**Estimated Study Completion Year**	**Clinical Trial[1]**	**Sponsor**
AMBROXOL	Inhibitory SMC for GCase	*GBA*-PD (10) PD (10)	Safety, Tolerability and PK/PD GCase and Ambroxol levels in blood and CSF	No	Phase II, completed	2018	NCT02941822 (AiM-PD)	University College, London and The Cure Parkinson's Trust
		PD Dementia (75)	Changes in ADAS-cog and ADAS-CGIC	Yes	Phase II, recruiting	2021	NCT02914366	Lawson Health Research Institute
		DLB (15)	Safety, Tolerability and PK/PD GCase and Ambroxol levels in blood and CSF MMSE	Yes	Phase I/II, not yet recruiting	2024	NCT04405596	Lawson Health Research Institute

		DLB (172)	Safety, Tolerability and PK/PD Changes in MMSE-NR3, ADCS-CGIC, CDR-SB, NPI, GDS	Yes	Phase II, not yet recruiting	2023	NCT04588285	Helse Fonna
LTI-291	Non-inhibitory SMC	PD and *GBA*-PD (40)	Safety, Tolerability and PK/PD	Yes	Phase I, completed	2018	Netherlands Trial Register: NTR6960	Lysosomal Therapeutics, Incorporated
		GBA-PD (15)	Safety, Tolerability and PK/PD	Yes	Phase I, follow up	2018	Netherlands Trial Register: NTR7299	Lysosomal Therapeutics, Incorporated
PR001A	AAV9-*GBA* delivery	*GBA*-PD (12)	Safety, Tolerability and PK/PD	No	Phase I/II, recruiting	2027	NCT04127578 (PROPEL)	Prevail Therapeutics
Venglustat GZ/SAR402671	Glucosylceramide synthase inhibitor	GBA-PD (270)	Change in MDS-UPDRS parts II & III	Yes	Phase II, active not recruiting	Halted in 2021	NCT02906020 (MOVES-PD)	Sanofi-Genzyme

AAV9, adeno-associated viral vector subtype 9; ADAS-CGIC, Alzheimer's Disease Assessment Scale-Clinician's Global Impression of Change; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; CDR-SB, Clinical Dementia Rating-Sum of Boxes; CSF, Cerebrospinal fluid; DLB, Dementia with Lewy Bodies; GBA, glucosylceramidase beta 1; GDS, geriatric depression scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MMSE, Mini Mental State Examination; MMSE-NR3, Mini Mental Status Examination, Norwegian revised version; NPI, neuropsychiatric inventory; PD, Parkinson Disease; PK/PD, Pharmacokinetics, and Pharmacodynamics; SMC, small molecule chaperone

[1] From ClinicalTrials.gov unless noted otherwise. Accessed April 2021.

7.3 Genetic Counselling

Genetic testing and counselling of *GBA* variants are not yet commonplace in clinical practice. The need for this is now urgent, long advocated by patient groups [196, 197]. Genetic counselling tailored to the nature of the *GBA* variant is required given its reduced penetrance and differential effects on PD risk and severity. PD penetrance in *GBA* mutation carriers represents a crucial yet unanswered issue for genetic counselling, especially for heterozygous carriers previously deemed to be a benign state [198]. The majority of people with biallelic or heterozygote *GBA* mutations do not develop PD; great care should be taken when counselling GD patients and their relatives about NDD risk factors. Estimated age-specific PD penetrance rates at 60 and 80 years of age are 4.7% and 9.1% in GD patients, 1.5% and 7.7% among heterozygote *GBA* mutation carriers, 0.7% and 2.1% among non-carriers, respectively [73]. Such findings largely concur with further studies, although discrepancies likely reflect differences in cohort size and methodology [129, 199-201]. Overestimation due to ascertainment bias pertaining to patient recruitment through a *GBA*/PD proband may explain reports of high rates of PD phenoconversion of ~30% in heterozygous *GBA* mutation carriers [198]. Intermediate penetrance rates of 10.0% and 19.4% at 60 and 80 years, respectively, were reported following the application of the kin-cohort method in unselected PD patients [202]. No significant difference in PD penetrance was detected between carriers of mild and severe *GBA* mutations [202]. Biomarker discovery programs (PPMI, BioFIND, PARS, RAPSODI, PREDICT-PD) conducting serial biochemical and clinical characterisations of prodromal *GBA*-PD patients offer an intriguing alternative approach to clarify the predictive value for PD penetrance of potential biomarkers [203].

To date, clinical relevance of carrying a *GBA* mutation remains limited for an individual. Large standard deviations in genotype-phenotype correlations of *GBA*-PD patients, complicating individualised predictions, must first be addressed to provide effective counselling [204]. However, clinical decision-making may benefit from verifying patient mutation status, with greater cognitive impairment observed in *GBA* variant carriers (60%) compared with non-carriers (6%) post deep brain stimulation [205]. Moreover, *GBA* mutation status may be relevant for entry into clinical trials, particularly for therapies targeting the *GBA* pathway.

With carrier screening for *GBA* mutations being increasingly more common, occurring via pre-conception screening in AJ populations and direct-to-consumer genetic tests, establishing a reliable means to determine individual PD risk is now critical. Future large-scale cohort studies are required to stratify PD risk according to specific *GBA* mutation [65]. Plans for more widespread use of genetic testing in PD creates an exciting time, facilitating the move towards personalised medicine.

8 Emerging Links

The discovery of *GBA* mutations as the greatest genetic risk factor for PD development informed our understanding of the mechanisms of cellular dysfunction leading to the onset of parkinsonism [4]. Causative for GD in biallelic form, the strikingly distinct allele-dependent clinical phenotype of

GBA mutations represents an interesting conundrum. Emerging evidence highlights further links between rare, mainly paediatric-onset AR diseases and common adult-onset NDDs presenting in heterozygous mutation carriers with incomplete penetrance [206]. Whilst the strongest evidence comes from *GBA* mutations, an excessive burden of LSD gene variants has been implicated in PD or parkinsonian-like degeneration [206]. *SMPD1*, *NAGLU*, *GALC*, *NPC1*, *ATP13A2* and *HEXB* mutations illustrate pleiotropic effects in heterozygous and biallelic states, with the latter resulting in Niemann-Pick disease, Sanfilippo syndrome B, Krabbe disease, Niemann-Pick type C, neuronal ceroid lipofuscinosis (NCL) and GM2 gangliosidosis, respectively [206]. Robak et al. [10] examined the variant burden of 54 LSD genes in 1156 PD cases and 1679 controls, highlighting *SLC17A5*, *ASAH1* and *CTSD* as novel candidate PD susceptibility genes. Disease rarity of non-*GBA* LSDs and lack of extensive patient registries has impeded definitive assessment of PD-associated genetic risk, likely requiring large-scale, well-matched, transethnic case control study cohorts.

Interestingly, this phenomenon extends beyond *GBA* and other LSD gene variants. In the 2012, Smith et al. [9] discovered that homozygous *GRN* mutations result in NCL, despite being a major cause of FTD with TDP-43 pathology in the heterozygous state. *GRN* loss-of-function mutations have been reported in AD [207], and more tentatively in amyotrophic lateral sclerosis and corticobasal degeneration [208, 209]. Carrier status of the AR Nasu-Hakola disease gene *TREM2* variant p.R47H, encoding a transmembrane receptor expressed on myeloid cells, confers a 2- to 4-fold increase in AD risk [210, 211] and is even associated with atypical FTD [212]. The identification of EIF2AK3 rs7571971 gene variant, pathogenic for the rare AR Wolcott-Rallison syndrome, as a significant risk factor for Progressive Supranuclear Palsy [13], and mitochondria AR disease-associated genes (*LMBRD1*, *MRPS34*, *CLN8*, *MPI* and *MUC1*) as contributors to PD risk and onset are further examples [14]. Elucidating the NDD risk associated with carrier status of AR disease genes is required for appropriate counselling of patients and their family members.

9 Conclusions

Significant progress has been made in our understanding of the link between *GBA* variants, PD and other synucleinopathies. Cellular mechanisms underlying *GBA*-PD and incomplete penetrance associated with *GBA* mutations remain incompletely understood. Therapeutics aiming to modulate the A-SYN/GCase relationship are under evaluation in clinical trials. Moreover, evidence from genetics, cell biology and epidemiology have unveiled a genetic association between AR disease genes and an increased risk of NDDs. *GBA* mutations are a key example of this recurring phenomenon, with further large-scale investigations likely to yield even more examples.

AUTHOR CONTRIBUTIONS

(1) Research project: A. Conception, B. Organization, C. Execution

(2) Manuscript Preparation: A. Writing of first draft, B. Review and Critique

S.R.L.V.: 1A, 1B, 1C, 2A, 2B

A.H.V.S.: 1A, 1B, 2B

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CONFLICT OF INTEREST

Both authors report no conflict of interest.

LEGEND TO FIGURE 1

FIGURE 1 *GBA* exonic structure and mutation distribution

FIGURE 2 The relationship between GCase and A-SYN. (A) In normal functioning lysosomes, wild-type (WT) GCase is synthesised, truncated and glycosylated in the endoplasmic reticulum (ER) and then trafficked through the trans-Golgi network via a GCase-LIMP2 complex. An interaction between GCase and the activator protein, Saposin C, is required for GCase to hydrolyse glucosylceramide (GlcCer) into glucose and ceramide. The possible mechanisms that GBA mutations lead to an increased risk of Parkinson disease (PD) are demonstrated in (B), (C) and (D). (B) demonstrates the gain-of-function hypothesis, where mutant GCase is retained in the ER leading to ER stress and increasing A-SYN aggregation. Degradation of A-SYN aggregates via autophagy or the ubiquitin-proteasome pathway is inhibited. (C) demonstrates a key feature of the loss-of-function hypothesis, where lysosomal GCase deficiency results in GlcCer accumulation, lipid dyshomeostasis and A-SYN aggregation. (D) demonstrates the GCase/A-SYN bidirectional feedback loop, whereby GCase deficiency promotes A-SYN oligomerisation, leading to even greater depletion of lysosomal GCase and further stabilisation of A-SYN oligomers by GlcCer accumulation.

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