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Featured Article

Association of glucocerebrosidase polymorphisms and mutations with dementia in incident Parkinson's disease

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Abstract

Introduction: Both polymorphisms and mutations in glucocerebrosidase (*GBA*) may influence the development of dementia in patients with Parkinson's disease.

Methods: Four hundred forty-two patients and 419 controls were followed for 7 years. Dementia was diagnosed using established criteria. Participants were analyzed for *GBA* genetic variants, including E326K, T369M, and L444P. Associations between *GBA* carrier status and dementia were assessed with Cox survival analysis.

Results: A total of 12.0% of patients with Parkinson's disease carried a *GBA* variant, and nearly half (22/53) of them progressed to dementia during follow-up. Carriers of deleterious *GBA* mutations (adjusted hazard ratio 3.81, 95% confidence interval 1.35 to 10.72; $P = .011$) or polymorphisms (adjusted hazard ratio 1.79; 95% confidence interval 1.07 to 3.00; $P = .028$) progressed to dementia more rapidly than noncarriers.

Discussion: *GBA* variants are of great clinical relevance for the development of dementia in Parkinson's disease, especially due to the relatively higher frequency of these alleles compared with other risk alleles.

Keywords: Parkinson's disease; Parkinson's disease with dementia; GBA; Longitudinal; Genetic association

1. Background

Dementia is among the most common and severe nonmotor symptoms of Parkinson's disease (PD), affecting nearly 20% of all patients within the first 5 years of the disease and most patients if they survive for more than 10 years after diagnosis [1,2]. Dementia in Parkinson's disease (PDD) has important adverse implications for quality of life, caregiver burden, and health-related costs [3]. The etiology of PDD remains poorly understood, and no neuroprotective therapies are currently available.

Genetic factors undoubtedly play a role in modifying the rate of disease progression in PD, and identifying these is a key to the early identification of patients at greatest risk of

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PDD. Genetic variants in glucocerebrosidase (*GBA*) have the strongest evidence for association with more rapid cognitive decline in PD. Homozygous mutations in *GBA* cause Gaucher disease (GD), and it is well established that some of the heterozygous mutations are associated with an increased risk of PD [4]. *GBA* variants associated with increased risk of PD chiefly fall into two categories: risk polymorphisms, the most common of which are E326K and T369M [5,6]; and deleterious mutations, such as N370S and L444P, which in a homozygous state cause GD [7].

GBA variants have been shown to increase the risk of PDD in cross-sectional studies [8,9], and longitudinal studies are starting to show how different *GBA* variants affect the rate of the development of dementia during the course of PD. Most longitudinal studies have found that carriers of deleterious *GBA* mutations are at increased risk of earlier PDD onset [10–13] or faster decline in global cognitive function [14]. To date, few studies have considered the effects of *GBA* risk polymorphisms on the development of PDD, and the only longitudinal studies to identify a significant association between *GBA* polymorphisms and progression to PDD did so only after controlling for the effect of *MAPT* genotype [10] or by including both mild cognitive impairment and PDD [6].

Therefore, we analyzed the *GBA* carrier frequencies of three deeply phenotyped, longitudinal PD cohorts of highly uniform design from Northern Europe, each of which uses established criteria for the diagnosis of PDD. Together, the Norwegian ParkWest study [15], the Parkinsonism Incidence in Northeast Scotland (PINE) [16], and the New Parkinson Patient in Umeå (NYPUM) [17] studies represent the largest prospective population-based longitudinal study of PD with age- and sex-matched controls in which the effect of *GBA* variants on PD progression has been addressed. By determining the roles of *GBA* polymorphisms and deleterious mutations in the development of PDD, we provide important insights into the heterogeneity of disease progression in these subgroups.

2. Methods

2.1. Study participants and procedures

The ParkWest study, the NYPUM project, and the PINE study were initiated between 2002 and 2004. All are large, on-going, population-based multicenter studies of newly diagnosed (incident) PD patients, designed to determine the incidence, neurobiology, and prognosis of PD and are described in detail elsewhere [15–18]. Briefly, 212 patients were enrolled in the ParkWest study, 211 in the PINE study, and 182 in the NYPUM study. Of these, 68 had a diagnosis other than PD during follow-up, 57 declined genotyping, 31 have no available DNA sample or DNA was not extractable, and seven did not consent to follow-up. The remaining 442 patients were eligible for this study and underwent comprehensive and standardized clinical examinations before drug treatment was initiated if possible (98% drug-naïve). During the same time, normal control subjects were recruited in the same geographical areas from spouses or friends of PD patients, or unrelated persons [19,20]. They were clinically examined and had no signs of movement disorders or cognitive deficiencies. Two hundred one controls were enrolled in the ParkWest study, 266 in the PINE study, and 56 in the NYPUM study. Of these, 68 had no DNA samples available or DNA was not extractable, 30 declined genotyping, and 6 developed incident PD during follow-up and were excluded. The remaining 419 consented to routine follow-up with a standardized battery of clinical testing. PD patients are currently under continued follow-up, and only those with a confirmed clinical or pathological (if performed postmortem) diagnosis of PD according to the UK brain bank criteria at their latest or final clinical visit were included. All participants signed written informed consent. The Western Norway Regional Committee for Medical and Health Research Ethics, the Regional Ethics Review Board in Umeå, and the Multi Centre Research Ethics Committee for Scotland approved the respective studies.

2.2. Clinical assessments in PD

The data were analyzed with the focus on PD risk, age at symptom onset or diagnosis, and the development of dementia. PD patients were examined at time of diagnosis by experienced study neurologists and research nurses. Clinical evaluations made up to the 7-year visit are included in this study. Motor severity was rated using the motor section (part III) of the Unified Parkinson Disease Rating Scale, and disease stage using the Hoehn and Yahr staging. Global cognitive decline was measured by the Mini–Mental State Examination [21]. Dementia diagnosis was set according to Movement Disorder Society criteria [22] (ParkWest and NYPUM) or Diagnostic and Statistical Manual of Mental Disorders, 4th Edition [23] (PINE), using a combination of clinical history from the patient and carer, and cognitive testing. Patients with dementia with Lewy bodies (DLBs), as defined by the development of dementia within 1 year of the onset of the motor features of PD, were not eligible for this study.

2.3. Genetic analysis

Genomic DNA was extracted from peripheral blood samples of eligible participants using standard methods. Large-scale allelic discrimination analysis was performed for all patients and controls using a predesigned TaqMan single nucleotide polymorphism genotyping assay for rs75548401/T369M, and custom assays for rs369068553/V460L, rs2230288/E326K, rs76763715/N370S, and rs781152868/Y135C (Thermo Fisher Scientific) as described [24,25]. The call rate was 99.8%.

A total of 188 patients of the ParkWest cohort were also characterized by whole exome sequencing (unpublished material). Variants falling within the *GBA* region were identified and analyzed using Ingenuity Variant Analysis (Qiagen, CA). Five nonsynonymous variants were detected: N370S, T369M, E326K, and two additional mutations, rs369068553/V460L and rs781152868/Y135C, which were confirmed by sequencing as described [26,27]. V460L and Y135C were genotyped in the remaining samples, and the carrier of V460L confirmed by sequencing.

For rs421016/L444P genotyping, a fragment of 960 base pairs was amplified as described (primer sequences and reaction conditions available on request) [26,28]. Polymerase chain reaction products were analyzed by restriction fragment length polymorphism in all three cohorts using *Nci*I [29]. Ten samples failed genotyping, giving a success rate of 98.8%. All mutations were confirmed by direct sequencing of the polymerase chain reaction product [29].

All amino acid substitutions are numbered excluding the 39-residue signal peptide.

2.4. Statistical methods

"*GBA* carriers" included all patients carrying any of the detected nonsynonymous *GBA* variants. *GBA* carriers were further split into "polymorphism carriers" (E326K, T369M, or V460L), and "deleterious carriers" (Y135C, N370S, or L444P), based on published reports and predicted pathogenicity as described [13].

Between-group differences were compared using t-tests, Mann-Whitney tests, and χ^2-tests as appropriate. For age of PD onset, we performed multiple linear regression analysis adjusted for study cohort and sex. We used logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for incident PD by different *GBA* carrier groups, without and with adjustment for study cohort, age at baseline, and sex. For incident PDD cases, we assigned time of dementia onset to the midpoint of the interval between assessments at which dementia was diagnosed, as described previously [1]. We performed Cox regression analysis to assess the role of *GBA* carrier status on the evolution of PDD in the patient group, adjusting for study cohort, age at baseline, sex, and years of education. Censoring occurred due to deaths and losses to follow-up, and at end of study, that is, at the 7-year visit. Assumption of proportionality was assessed and deemed to hold using log–log plots. There was no statistical evidence of differential effect of *GBA* on PDD-free survival between cohorts. We considered two-tailed values of $P < .05$ significant and conducted all statistical analyses using IBM SPSS Statistics (Armonk, NY), version 21.0.

3. Results

Of 861 study participants, 419 were controls, and 442 were patients with PD. Their baseline characteristics are listed in Table 1. No statistical differences were detected between patients and controls in any demographic or clinical variables at baseline, apart from family history of PD and years of education ($P < .001$). For PD patients, mean age at baseline was 69.81 (±9.62) years, with 60.4% (267) males. During follow-up, 115 (26.0%) patients deceased, whereas 24 (5.4%) patients dropped out of the study for reasons other than death (Fig. 1).

3.1. Genetic analysis

We identified a total of 82 carriers of *GBA* variants in this cohort (Supplementary Table 1). In addition to analysis of the four most frequently studied *GBA* variants in PD, E326K, T369M, N370S, and L444P, whole exome sequencing of patients from ParkWest identified two further mutations: V460L, previously identified in PD and healthy controls [30,31] and; Y135C, which has been identified in GD (ClinVar accession 280972) but not PD.

One patient was homozygous for E326K, and one patient carried both the E326K and the T369M variant. No other homozygous subjects or carriers of complex alleles were identified. For further analysis, patients and controls were classified as noncarriers or carriers of any *GBA* variant, or further subdivided into carriers of polymorphisms or carriers of deleterious mutations (Table 2 and Supplementary Table 1).

3.2. GBA and PD risk

Of the 82 *GBA* carriers in the cohort, 53 were patients (12.0% of patients) and 29 controls (6.9% of controls). Logistic regression analysis showed that both carriers of any *GBA* variant and carriers of polymorphisms had an increased risk of PD (all *GBA* carriers OR 1.83; 95% CI 1.14 to 2.94; $P = .012$, and polymorphism carriers OR 1.73; 95% CI 1.05 to 2.86; $P = .033$). After adjusting for study cohort, age, and sex, the associations remained significant for carriers of any *GBA* variant (all *GBA* carriers: OR 1.70; 95% CI 1.05 to 2.77; $P = .032$, and polymorphism carriers: OR 1.63; 95% CI 0.97 to 2.73; $P = .065$). Furthermore, linear regression analysis revealed a significant effect of *GBA* variants on age of PD diagnosis, reducing age at onset by 3.4 years on average in patients with any *GBA* variant ($\beta = -3.38$; 95% CI − 6.13 to −0.63; $P = .016$) and 9.1 years in patients with a deleterious mutation ($\beta = -9.10$; 95% CI −15.80 to −2.40; $P = .008$), compared with noncarriers (70.2 ± 9.50 years). These associations remained significant when adjusting for study cohort and sex (all *GBA* carriers: $\beta = -3.55$; 95% CI −6.28 to −0.81; $P = .011$, and mutation carriers: $\beta = -9.56$; 95% CI −16.23 to −2.88; $P = .005$). No associations were identified between *GBA* carrier status and demographic or clinical baseline variables other than age (all $P > .050$) (Table 2).

Table 1
Baseline characteristics and duration of follow-up of the patients and controls included in the study

	ParkWest		PINE		NYPUM		All	
Clinical variables	NC	PD	NC	PD	NC	PD	NC	PD
N total*	192	190	171	118	56	134	419	442
Male, N (%)	97 (50.5)	115 (60.5)	109 (63.7)	72 (61.0)	38 (67.9)	80 (59.7)	244 (58.2)	267 (60.4)
Age at baseline, years, mean (±SD)	66.26 (9.53)	67.96 (9.11)	74.79 (9.32)	72.16 (9.89)	64.84 (7.72)	70.37 (9.61)	69.55 (10.19)	69.81 (9.62)
Age at first symptoms, mean (±SD)		65.68 (9.21)		69.98 (9.87)		68.43 (9.67)		67.67 (9.68)
≤65 years at baseline, N (%)	82 (42.7)	69 (36.3)	24 (14.0)	27 (22.9)	26 (46.4)	43 (32.1)	132 (31.5)	139 (31.4)
Positive family history, N (%)†	31 (16.1)	42 (22.1)	9 (5.3)	24 (20.3)	0‡	38 (28.4)	40 (9.5)	104 (23.5)
Education, years mean (±SD)	12.22 (3.70)	11.13 (3.30)	12.84 (1.64)	13.36 (1.90)	11.94 (3.85)	9.92 (3.83)	12.46 (3.02)	11.42 (3.40)
UPDRS III, mean (±SD)§	-	23.54 (11.24)	-	24.12 (11.60)	-	26.83 (11.29)	-	24.69 (11.41)
Hoehn and Yahr, mean (±SD)§	-	1.92 (0.63)	-	2.22 (0.76)	-	2.26 (0.69)	-	2.10 (0.70)
MMSE score, mean (±SD)	28.56 (1.49)	27.73 (2.40)	28.84 (1.18)	28.43 (1.64)	29.24 (0.83)	28.60 (1.44)	28.20 (2.18)	28.17 (2.00)
Duration of follow-up, years, mean (±SD)	5.96 (2.18)	6.34 (1.58)	5.97 (1.63)	5.92 (1.74)	3.1 (3.6)	6.38 (1.36)	5.97 (1.95)	6.24 (1.57)

Abbreviations: *GBA*, glucocerebrosidase; MMSE, Mini–Mental State Examination; NA, not available; NC, normal controls; NYPUM, the New Parkinson Patient in Umeå project; ParkWest, the Norwegian ParkWest study; PD, patients with Parkinson disease; PINE, the Parkinsonism incidence in Northeast Scotland study; SD, standard deviation; UPDRS III, Unified Parkinson Disease Rating Scale Part III.

*N total gives the number for which *GBA* genotyping was performed.

†Self-reported family history.

‡Available for 30/56 controls where none had a positive family history for PD.

§UPDRS III and Hoehn and Yahr were not measured in control subjects.

3.3. GBA and PDD risk

Progression to PDD was more frequent in the *GBA* carrier group compared with noncarriers. By 7 years of follow-up, 22 (41.5%) of the 53 *GBA* carriers had progressed to dementia versus 107 (27.5%) of the 389 noncarriers. To assess the longitudinal effects of *GBA* carrier status on progression to dementia, we performed a Cox regression analysis (Table 3, Fig. 2). We observed a significant association between *GBA* carrier status and progression rate to dementia when adjusting for age at baseline, years of education, study cohort, and sex (HR 1.98, 95% CI 1.23 to 3.18, $P = .005$). When assessed separately, the polymorphism carrier group showed a significant but more moderate association with progression rate to dementia (adjusted HR 1.79, 95% CI 1.07 to 3.00, $P = .028$), whereas the deleterious carriers had a higher risk of a progression to dementia (adjusted HR = 3.81, 95% CI 1.35 to 10.72, $P = .011$) than noncarriers. Adjusting with covariables strengthened the effect of *GBA* on progression to PDD (Table 3). Most of the adjusting effect comes from including age at onset in the models, suggesting that the observed, unadjusted effect of *GBA* on PDD risk is attenuated by the additional effect that *GBA* carriers tend to be younger at onset of PD than noncarriers.

The effect of *GBA* on PDD was not reflected by an overall increased rate of disease progression, as we observed no significant differences in the progression of Hoehn and Yahr scores between *GBA* carriers and noncarriers during the first 7 years of disease, or between any of the *GBA* subgroups and noncarriers (all $P > .35$, data not shown).

4. Discussion

In this study, we examined the association of *GBA* variants with the development of dementia in the largest population-based longitudinal multicenter study of incident PD to date. We showed that PD patients carrying *GBA* variants have a faster progression to dementia, with carriers of deleterious mutations displaying a more rapid disease progression than carriers of *GBA* polymorphisms.

Of the 129 patients who progressed to PDD within the 7-year visit, 17.1% were carriers of a *GBA* variant, compared with 9.9% of the PD patients without dementia. We observed a differential effect of the type of *GBA* variant on the risk for dementia; multivariable survival analysis showed that the risk of progressing to PDD within the 7-year visit for *GBA* polymorphism carriers was nearly doubled compared with noncarriers, whereas deleterious mutation carriers were at nearly four times greater risk.

The role of *GBA* polymorphisms in disease heterogeneity as PD progresses is a disputed topic: The first longitudinal study to analyze *GBA* found that mutations predicted increased risk of dementia, but when comparing seven polymorphism carriers to 117 noncarriers, an association with dementia was only found after adjusting for *MAPT* haplotype [10]. Subsequently, two studies found that E326K is associated with a higher prevalence of dementia [8], or with conversion to mild cognitive impairment or dementia [6], but unexpectedly in these studies, carriers of *GBA* mutations were at similar or lower risk than E326K carriers. Conversely, a Spanish retrospective study observed increased risk of PDD in *GBA* mutation carriers, but no effect in patients carrying potentially benign variants [13]. However, the benign group

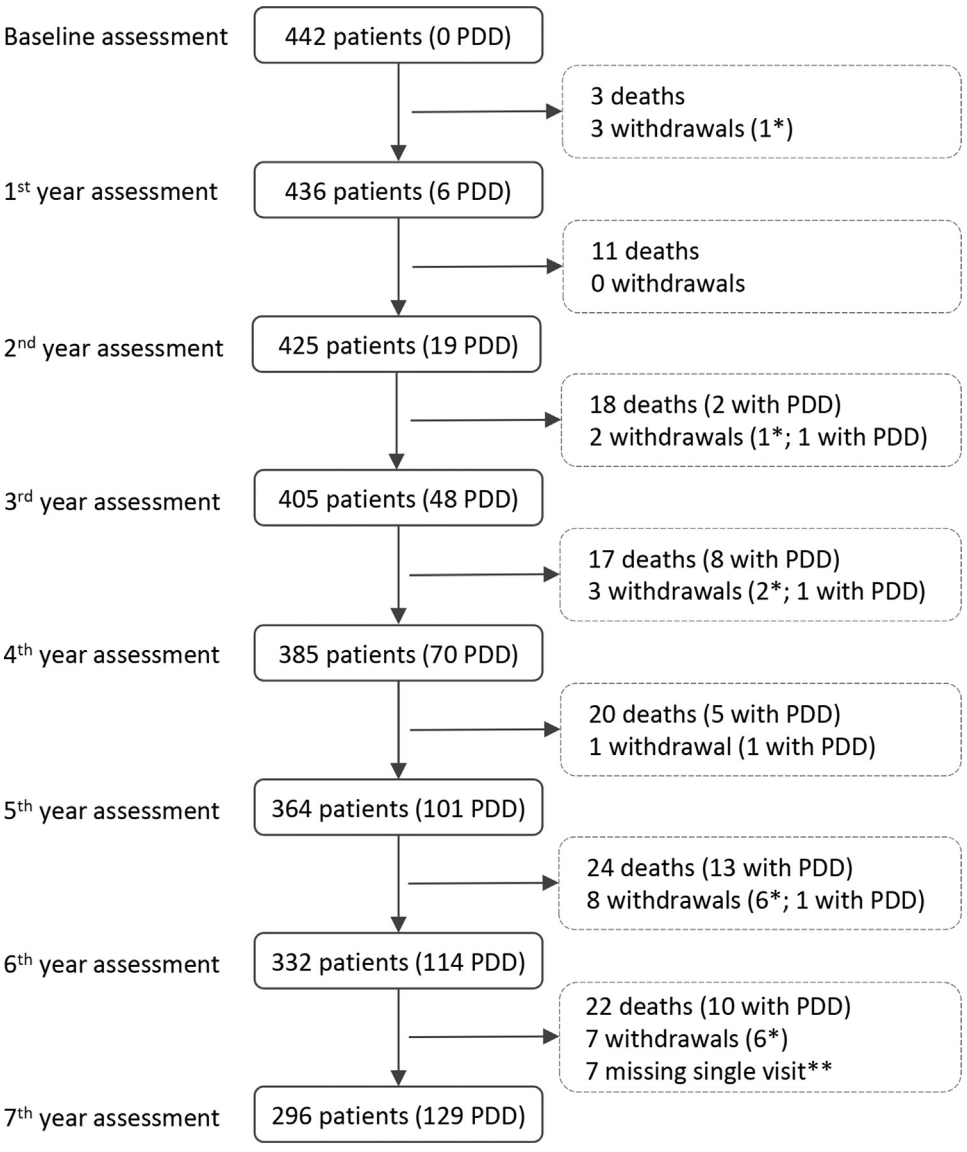


Fig. 1. Flowchart of patient inclusion over time in this study. Overview of patient inclusion from baseline until the 7-year visit. The number of patients attending each visit is shown, and the cumulative number of patients diagnosed with PDD is shown in brackets. Withdrawals and deaths between visits are shown in dashed boxes. *Withdrew from study visits but dementia and death status known. **Seven patients had not yet attended the 7-year visit but were not lost to the study. The flowchart is simplified for readability. Abbreviation: PDD, dementia in Parkinson's disease.

included 13 synonymous and noncoding sequence variants in addition to E326K and T396M, which could mask the effect of missense variants. The largest multicenter study to date to analyze the role of polymorphisms did not find an effect on PDD risk; however, this study did estimate a small increased risk associated with cognitive decline (6.6% of patients; HR 1.36, 95% CI 0.89 to 2.05) [14]. Of notable difference to our study was the considerable younger PD sample as well as the use of Mini–Mental State Examination for the detection of PDD, which has lower sensitivity compared with established diagnostic criteria for PDD [32]. Considering these inconsistent findings, this study, which is composed of cohorts specifically designed to study the incidence and prognosis of PD, provides new and important insights into the role of *GBA* polymorphisms in PDD.

Significant attention has been paid to the phenotypic characterization of PD patients with the most frequent pathogenic *GBA* mutations [10–14,33,34], and our findings reaffirm the role of damaging mutations in the development of dementia in PD. The clinical relevance of these results is augmented by the additional effect of *GBA* carrier status on age at PD onset: We show that in addition to more rapid dementia development, patients with PD who carried a *GBA* variant had a younger age of onset. The largest difference was observed in carriers of *GBA* mutations who were on average 9 years younger at diagnosis than noncarriers. This is noteworthy as idiopathic PD patients with a younger age of onset typically have a more benign disease course with slower motor and cognitive decline, when compared with patients with later onset PD [35,36].

Table 2
Demographic and clinical baseline features of patients with PD

Clinical variables	Noncarriers	*GBA* carriers	*P**	Polymorphism carriers	*P**	Deleterious mutation carriers	*P**
Male, N (%)	233 (59.9)	34 (64.2)	.654	28 (62.2)	.873	6 (75.0)	.486
Age at baseline, mean (±SD)	70.22 (9.49)	66.84 (10.07)	**.016**	67.84 (10.27)	.115	61.21 (6.97)	**.008**
Age at first symptoms, mean (±SD)	68.03 (9.63)	64.98 (9.79)	**.031**	65.95 (10.06)	.172	59.54 (5.90)	**.013**
Positive family history, N (%)	93 (23.9)	11 (20.8)	.861	10 (22.2)	1.000	1 (12.5)	.686
Education, years, mean (±SD)	11.39 (3.44)	11.63 (3.17)	.637	11.61 (3.22)	.693	11.75 (3.06)	.768
UPDRS III, mean (±SD)	24.99 (11.63)	22.49 (9.52)	.135	23.00 (9.72)	.271	19.63 (8.26)	.195
Hoehn and Yahr, mean (±SD)	2.11 (0.72)	2.08 (0.61)	.761	2.09 (0.62)	.871	2.0 (0.60)	.676
MMSE score, mean (±SD)	28.15 (2.05)	28.34 (1.62)	.532	28.36 (1.69)	.530	28.25 (1.28)	.892

Abbreviations: *GBA*, glucocerebrosidase; MMSE, Mini–Mental State Examination; PD, Parkinson disease; SD, standard deviation; UPDRS III, Unified Parkinson Disease Rating Scale Part III.

NOTE. Significant *P* values (<.05) are highlighted in bold.

*Unadjusted *P* values were calculated using *t*-tests, Mann-Whitney *U*-tests, and χ^2-tests as appropriate.

Information on the frequency of *GBA* variants in Northern Europe is scarce. Previous studies reported a low carrier frequency of genetic variants in PD patients, with the exception of L444P in Northern Sweden, which is more prevalent in this region consistent with a higher incidence of GD in this part of the country [25,29,37]. Here we performed complete screening of *GBA* in a population-based cohort of PD patients from Norway and found a comparatively high frequency of *GBA* variants (12.0%). These results are similar to the overall *GBA* carrier frequency in other studies of European PD patients that have employed complete screening of *GBA* (range 9.3%–12.2 %) [9,10,13,34] and highlight the importance of complete sequencing and cataloging of all variants in population-based cohorts to avoid underestimating variant frequency. Although not the main focus of this study, we further show that both carriers of any variant and polymorphism carriers were at increased risk of PD. These data reinforce the role of T369M and E326K as risk factors in PD [5,37,38] and extend the finding that *GBA* is a major risk factor in PD to Northern European populations [25].

This work has considerable strengths: Each study is a representative incident cohort, designed to identify all new PD cases in a given population early in their disease, with high levels of consent and low levels of losses to follow-up for reasons other than death (Fig. 1). Furthermore, each study made substantial efforts to follow-up all participants until death, including home visits for those no longer willing or able to attend clinic visits, and telephone follow-up for dropouts, greatly reducing the problem of selection bias. Of equal importance are the uniformities in data-ascertainment methods, with each study center using validated criteria to diagnose dementia, and a median prospective follow-up period of 7 years from PD diagnosis. These methods minimize the risk of erroneous inclusion of non-PD cases and provide information about individual conversion to PDD from the time of PD diagnosis. Potential limitations of our study include the modest number of carriers of individual variants, which prevented us from analyzing the effect of each variant separately. In the future, it will be important to determine if individual *GBA* polymorphisms have differential effects on disease severity, as no comparisons between E326K and T369M have been performed in unselected PD populations. This will require further pooling of existing cohorts to give larger numbers or studying inception cohorts enriched for carriers of different *GBA* variants. Furthermore, this study was designed to study the development of PDD, and patients with DLB were excluded. Given that DLB and PDD share many pathological and clinical features, and probably represent two clinical entities on a spectrum of Lewy body disease, it will be of great interest to determine how different types of *GBA* variants affect disease progression in DLB. Finally, complete information on the development of dementia in the control population during follow-up was not available, preventing the analysis of the role of *GBA* in the non-PD population.

Dementia typically occurs in advanced stages of idiopathic PD and is often related to the advanced spread of

Table 3
Survival analysis for dementia on the disease duration timescale

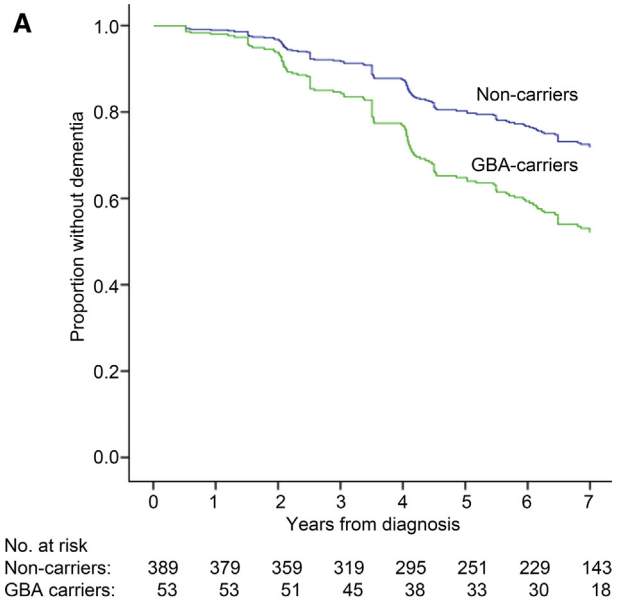
GBA carrier status	Total PD, n	PDD, n	% PDD	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)*	*P*
Noncarriers	389	107	27.5	Ref†		Ref†	
GBA carriers	53	22	41.5	1.53 (0.97–2.43)	.068	1.98 (1.23–3.18)	**.005**
Polymorphism carriers	45	18	40.0	1.48 (0.90–2.44)	.124	1.79 (1.07–3.00)	**.028**
Deleterious mutation carriers	8	4	50.0	1.82 (0.67–4.94)	.242	3.81 (1.35–10.72)	**.011**

Abbreviations: CI, confidence interval; *GBA*, glucocerebrosidase; HR, hazard ratio; PD, Parkinson disease; PDD, Parkinson disease with dementia.

NOTE. Significant *P* values (<.05) are highlighted in bold.

*Adjusted for study cohort, sex, age at baseline, and years education.

†Noncarrier group used as reference group for statistical analysis.



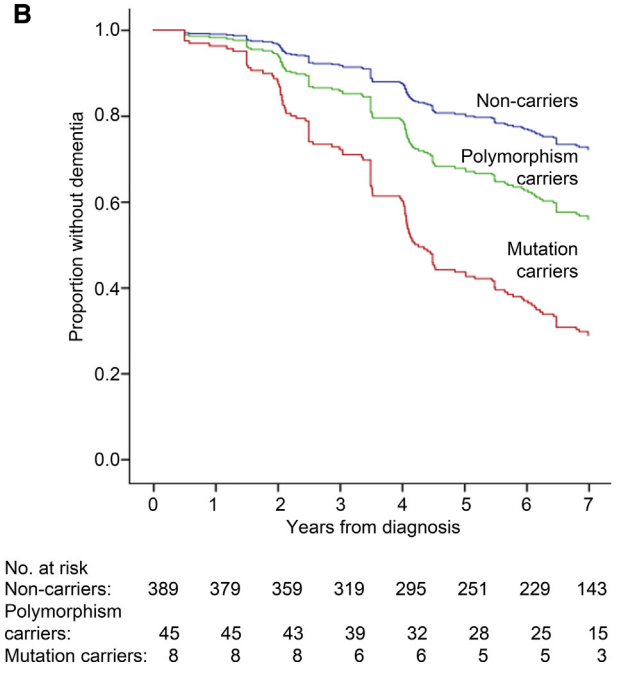


Fig. 2. Survival analysis for dementia onset. Cox regression models show the effects of *GBA* carrier status on the outcome of dementia over time in patients with PD, with adjustment for covariates (study cohort, age, sex, and years of education). (A) Analysis of time to PDD for noncarriers and patients with *GBA* variants, or (B) noncarriers and patients with deleterious *GBA* mutations or polymorphic variants. Abbreviations: PDD, Dementia in Parkinson disease; *GBA*, glucocerebrosidase; PD, Parkinson disease.

Lewy bodies to cortical areas. Reduced *GBA* enzyme activity leads to accumulation and oligomerization of α-synuclein. Several studies have shown that the effect of *GBA* variants on enzyme activity varies according to the nature of the variant: individuals with *GBA* mutations display the lowest *GBA* activity, whereas polymorphism carriers display a level of activity intermediate between noncarriers and mutants [39,40]. This suggests a disease mechanism by which *GBA* mutations ultimately drive the development of dementia by increasing the accumulation and spread of α-synuclein. In support of this, autopsies of *GBA* mutation-carriers revealed a more widespread Lewy body–type pathology in the neocortex than that of matched PD controls [27]. Our work suggests that polymorphic variants also play a role in the hastened development of PDD, although the effect on *GBA* activity might be milder, and the subsequent rate of α-synuclein accumulation and spread lower, leading to the observed milder disease phenotype. A range of different studies, including imaging and histopathological analyses of brains, and animal studies, will be required to improve understanding of precisely how each *GBA* variant increases the risk of cognitive decline and affects the underlying spread of Lewy body pathology in PD.

5. Conclusion

In this population-based study, we present the first comprehensive overview of *GBA* variants in Northern Europe and show that in our unselected multicenter cohort of patients with incident PD, *GBA* carrier status has important implications for the development of dementia. Given that variants in *GBA* are present in 12% of the PD population in this study, this places many individuals at risk of a more severe disease course. At present, there are no preventative PD treatments that target *GBA* pathways, and an individual's *GBA* status does not alter clinical management, which contend that screening for *GBA* variants should not yet be included in routine genetic testing in a clinical setting. However, future studies should focus on establishing the success of combining *GBA* mutations and polymorphisms with other predictors of dementia to gain a more precise indication of when PD patients develop dementia. The ability to predict the development of dementia is highly relevant for recruitment into and stratification of clinical trials, and the finding in this study that PD patients harboring either *GBA* mutations or polymorphisms are at significantly increased risk of early PDD, advocates that both groups of patients are candidates for clinical PDD research studies. This will be especially important as interventions that target *GBA* to slow disease progression and to prevent dementia become available.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.04.006.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed and identified all studies in which the role of glucocerebrosidase (*GBA*) variants on the development of dementia in Parkinson's disease was addressed. These mainly focused on the role of *GBA* mutations, and the question of whether *GBA* polymorphisms modify the development of dementia in Parkinson's disease remains unresolved.
2. Interpretation: Our findings show clearly, for the first time, that both carriers of *GBA* mutations and polymorphisms are at increased risk of developing dementia during the first 7 years of Parkinson's disease.
3. Future directions: The article proposes that carriers of both *GBA* mutations and polymorphisms should be considered for inclusion in future clinical trials targeting GCase dysfunction. This will require (1) establishment of the size of effect of each polymorphism on the rate of disease progression in larger cohorts; and (2) functional studies to determine the effect of each polymorphism of GCase activity.

References

[1] Pedersen KF, Larsen JP, Tysnes OB, Alves G. Natural course of mild cognitive impairment in Parkinson disease: a 5-year population-based study. Neurology 2017;88:767–74.
[2] Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson disease. J Neurol Sci 2010;289:18–22.
[3] Vossius C, Larsen JP, Janvin C, Aarsland D. The economic impact of cognitive impairment in Parkinson's disease. Movement Disord 2011; 26:1541–4.
[4] Sidransky E, Lopez G. The link between the GBA gene and parkinsonism. Lancet Neurol 2012;11:986–98.
[5] Mallett V, Ross JP, Alcalay RN, Ambalavanan A, Sidransky E, Dion PA, et al. GBA p.T369M substitution in Parkinson disease: polymorphism or association? A meta-analysis. Neurol Genet 2016; 2:e104.
[6] Davis MY, Johnson CO, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, et al. Association of GBA mutations and the E326K polymorphism with motor and cognitive progression in Parkinson disease. JAMA Neurol 2016;73:1217–24.
[7] Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. N Engl J Med 2009;361:1651–61.
[8] Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, et al. GBA variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord 2016;31:95–102.
[9] Seto-Salvia N, Pagonabarraga J, Houlden H, Pascual-Sedano B, Dols-Icardo O, Tucci A, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord 2012;27:393–9.
[10] Winder-Rhodes SE, Evans JR, Ban M, Mason SL, Williams-Gray CH, Foltynie T, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 2013;136:392–9.
[11] Oeda T, Umemura A, Mori Y, Tomita S, Kohsaka M, Park K, et al. Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. Neurobiol Aging 2015;36:3306–13.
[12] Cilia R, Tunesi S, Marotta G, Cereda E, Siri C, Tesei S, et al. Survival and dementia in GBA-associated Parkinson's disease: the mutation matters. Ann Neurol 2016;80:662–73.
[13] Jesús S, Huertas I, Bernal-Bernal I, Bonilla-Toribio M, Cáceres-Redondo MT, Vargas-González L, et al. GBA variants influence motor and non-motor features of Parkinson's disease. PLoS One 2016; 11:e0167749.
[14] Liu G, Boot B, Locascio JJ, Jansen IE, Winder-Rhodes S, Eberly S, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. Ann Neurol 2016;80:674–85.
[15] Alves G, Muller B, Herlofson K, HogenEsch I, Telstad W, Aarsland D, et al. Incidence of Parkinson's disease in Norway: the Norwegian ParkWest study. J Neurol Neurosurg Psychiatry 2009;80:851–7.
[16] Caslake R, Taylor K, Scott N, Gordon J, Harris C, Wilde K, et al. Age-, gender-, and socioeconomic status-specific incidence of Parkinson's disease and parkinsonism in northeast Scotland: the PINE study. Parkinsonism Relat Disord 2013;19:515–21.
[17] Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. Mov Disord 2010;25:341–8.
[18] Backstrom D, Eriksson Domellof M, Granasen G, Linder J, Mayans S, Elgh E, et al. Polymorphisms in dopamine-associated genes and cognitive decline in Parkinson's disease. Acta Neurol Scand 2018;137:91–8.
[19] Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves GNorwegian ParkWest Study G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009; 72:1121–6.

[20] Fielding S, Macleod AD, Counsell CE. Medium-term prognosis of an incident cohort of parkinsonian patients compared to controls. Parkinsonism Relat Disord 2016;32:36–41.
[21] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
[22] Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007;22:1689–707; quiz 837.
[23] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV (text revision) 2000. Washington DC: American Psychological Association; 2000.
[24] Lange J, Lunde KA, Sletten C, Moller SG, Tysnes OB, Alves G, et al. Association of a BACE1 gene polymorphism with Parkinson's disease in a Norwegian population. Parkinsons Dis 2015;2015:973298.
[25] Berge-Seidl V, Pihlstrøm L, Maple-Grødem J, Forsgren L, Linder J, Larsen JP, et al. The GBA variant E326K is associated with Parkinson's disease and explains a genome-wide association signal. Neurosci Lett 2017;658:48–52.
[26] Stone DL, Tayebi N, Orvisky E, Stubblefield B, Madike V, Sidransky E. Glucocerebrosidase gene mutations in patients with type 2 Gaucher disease. Hum Mutat 2000;15:181–8.
[27] Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 2009;132:1783–94.
[28] Torok R, Zadori D, Torok N, Csility E, Vecsei L, Klivenyi P. An assessment of the frequency of mutations in the GBA and VPS35 genes in Hungarian patients with sporadic Parkinson's disease. Neurosci Lett 2016;610:135–8.
[29] Toft M, Pielsticker L, Ross OA, Aasly JO, Farrer MJ. Glucocerebrosidase gene mutations and Parkinson disease in the Norwegian population. Neurology 2006;66:415–7.
[30] Kalinderi K, Bostantjopoulou S, Paisan-Ruiz C, Katsarou Z, Hardy J, Fidani L. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Greece. Neurosci Lett 2009;452:87–9.
[31] Gan-Or Z, Mirelman A, Postuma RB, Arnulf I, Bar-Shira A, Dauvilliers Y, et al. GBA mutations are associated with rapid eye movement sleep behavior disorder. Ann Clin Transl Neurol 2015;2:941–5.
[32] Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology 2009;73:1738–45.
[33] Brockmann K, Srulijes K, Pflederer S, Hauser AK, Schulte C, Maetzler W, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord 2015;30:407–11.
[34] Crosiers D, Verstraeten A, Wauters E, Engelborghs S, Peeters K, Mattheijssens M, et al. Mutations in glucocerebrosidase are a major genetic risk factor for Parkinson's disease and increase susceptibility to dementia in a Flanders-Belgian cohort. Neurosci Lett 2016;629:160–4.
[35] Kempster PA, O'Sullivan SS, Holton JL, Revesz T, Lees AJ. Relationships between age and late progression of Parkinson's disease: a clinico-pathological study. Brain 2010;133:1755–62.
[36] Wickremaratchi MM, Ben-Shlomo Y, Morris HR. The effect of onset age on the clinical features of Parkinson's disease. Eur J Neurol 2009;16:450–6.
[37] Ran C, Brodin L, Forsgren L, Westerlund M, Ramezani M, Gellhaar S, et al. Strong association between glucocerebrosidase mutations and Parkinson's disease in Sweden. Neurobiol Aging 2016;45. 212.e5-212.e11.
[38] Pankratz N, Beecham GW, DeStefano AL, Dawson TM, Doheny KF, Factor SA, et al. Meta-analysis of Parkinson's disease: identification of a novel locus, RIT2. Ann Neurol 2012;71:370–84.
[39] Pchelina S, Emelyanov A, Baydakova G, Andoskin P, Senkevich K, Nikolaev M, et al. Oligomeric alpha-synuclein and glucocerebrosidase activity levels in GBA-associated Parkinson's disease. Neurosci Lett 2017;636:70–6.
[40] Montfort M, Chabas A, Vilageliu L, Grinberg D. Functional analysis of 13 GBA mutant alleles identified in Gaucher disease patients: pathogenic changes and "modifier" polymorphisms. Hum Mutat 2004;23:567–75.