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ORIGINAL ARTICLE

Prevalence and genotype–phenotype correlations of *GBA*-related Parkinson disease in a large Chinese cohort

Jingru Ren[1] | **Ronggui Zhang**[1] | **Chenxi Pan**[1] | **Jianxia Xu**[1] | **Haochen Sun**[1] | **Ping Hua**[1] | **Li Zhang**[2] | **Wenbin Zhang**[3] | **Pingyi Xu**[4] | **Changyan Ma**[5] | **Weiguo Liu**[1]

[1]Department of Neurology, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[2]Department of Geriatrics, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[3]Department of Neurosurgery, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, China

[4]Department of Neurology, First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[5]Department of Medical Genetics, Nanjing Medical University, Nanjing, China

Correspondence
Weiguo Liu, Department of Neurology, The Affiliated Brain Hospital of Nanjing Medical University, 264 Guangzhou Road, Gulou District, Nanjing 210029, China.
Email: wgliunbh@sina.com

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Abstract

Background and purpose: Variants in the glucocerebrosidase (*GBA*) gene are recognized as a common and important genetic risk factor for Parkinson disease (PD). However, the impact of variant severity on the clinical phenotype of PD in the Chinese population remains unclear. Thus, the present study aimed to determine the frequency of *GBA*-related PD (*GBA*-PD) and the relationship of *GBA* variant severity with clinical characteristics in a large Chinese cohort.

Methods: Long-range polymerase chain reaction and next generation sequencing were performed for the entire *GBA* gene. *GBA* variant severity was classified into five classes: mild, severe, risk, complex, and unknown.

Results: Among the total 737 PD patients, 47 *GBA* variants were detected in 79 (10.72%) patients, and the most common *GBA* variants were R163Q, L444P, and R120W. Complete demographic and clinical data were obtained for 673 patients, which revealed that 18.50% of early onset PD patients had *GBA* variants. Compared with patients without *GBA* variants, *GBA*-PD patients experienced PD onset an average of 4 years earlier and had more severe motor and nonmotor symptoms. Patients carrying severe and complex variants had a higher burden of nonmotor symptoms, especially depression, and more mood/cognitive and gastrointestinal symptoms than patients carrying mild variants.

Conclusions: *GBA*-PD is highly prevalent in the Chinese population. The severity of *GBA* variants underlies distinct phenotypic spectrums, with PD patients carrying severe and complex variants seeming to have similar phenotypes. PD patient stratification by *GBA* variant severity should become a prerequisite for selecting specific treatments.

KEYWORDS
GBA, genotype–phenotype correlations, Parkinson disease, prevalence

INTRODUCTION

Parkinson disease (PD) is a chronic progressive neurodegenerative disorder defined by the loss of dopaminergic neurons in the substantia nigra and the presence of alpha-synuclein (α-syn) protein aggregation [1,2]. It is well known that genetic factors influence PD susceptibility, especially variants in the glucocerebrosidase (*GBA*) gene [3,4]. Heterozygous variants in the *GBA* gene, which encodes the lysosomal enzyme β-glucocerebrosidase (GCase) that hydrolyzes glucocerebroside to glucose and ceramide, are recognized as the most common and important genetic risk factor for sporadic PD, increasing the risk of developing PD by 5%–30% [5–8].

It is estimated that 7%–15% of PD patients worldwide harbor a heterozygous *GBA* variant. However, due to ethnic heterogeneity in *GBA* variants, the frequency of *GBA* variants varies greatly between populations, ranging from 10%–31% in the Ashkenazi Jewish (AJ) population to 3%–12% in non-AJ North Americans and 2.1%–8.7% in the Chinese population [9–12]. Notably, the presence of a highly homologous pseudogene (*GBAP1*), which is located 16 kb downstream of the functional *GBA* gene with 96% of the shared exon sequence, makes *GBA* sequencing challenging [13,14]. As a result, most studies are limited to screening the most common *GBA* variants, such as L444P and N370S [15–18], and the prevalence may thus be underestimated.

Overall, *GBA*-related PD (*GBA*-PD) patients have earlier onset, higher prevalence of the postural instability gait difficulty (PIGD) phenotype, worse motor symptoms, more frequent nonmotor symptoms (NMSs; especially cognitive impairment), more rapid progression, and reduced survival compared with non-*GBA*-mutated PD (NM-PD) patients [17,19–22]. A recent study explored the impact of *GBA* status on the clinical phenotype of PD in the Italian population, and found that different variant types exhibited distinct phenotypic characteristics [23]. To the best of our knowledge, studies linking the severity of different *GBA* variants to clinical features in the Chinese PD population have not been performed previously, so the genotype–phenotype correlations of *GBA*-PD patients cannot be fully elucidated.

In the present study, the entire *GBA* gene was screened in a large cohort of Chinese PD patients. We then conducted a comprehensive comparison of demographic, motor, and nonmotor characteristics in PD patients with and without *GBA* variants, as well as in patients with *GBA* variants of varying severity in the *GBA*-PD group.

METHODS

Participants

From January 2012 to June 2020, a total of 737 unrelated Chinese PD patients were recruited at the Department of Neurology of the Affiliated Brain Hospital of Nanjing Medical University. All patients participating in this study were evaluated by a movement disorder specialist and diagnosed with PD based on the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [24]. The exclusion criteria for this study were as follows: (i) atypical or secondary parkinsonism; (ii) severe chronic diseases such as heart failure, kidney failure, etc.; and (iii) clinically significant lesions revealed by brain magnetic resonance imaging. This study was approved by the Medical Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (2011-KY003, 2015-KY030, and 2019-KY019-01) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants before starting the experiment.

Clinical assessment

We successfully collected demographic, motor, and nonmotor characteristics for 673 of the 737 patients. The demographic data included age, gender, years of formal education, age at onset, frequency of early onset PD (EOPD), family history for PD, years of disease duration, and levodopa equivalent daily dose (LEDD). The age at onset in PD patients was defined as the age when motor symptoms first appeared. Patients with an age at onset of ≤50 years were classified as EOPD [25]. Information about dopaminergic drug use was collected, and the LEDD was calculated [26]. The evaluated motor features included the Unified Parkinson's Disease Rating Scale (UPDRS) part II, UPDRS part III, and modified Hoehn-Yahr (H-Y) stage, which reflect activities of daily living (ADL), motor disability, and severity of disease, respectively. According to the formula proposed by Jankovic et al. [27], PD patients were divided into tremor-dominant (TD), indeterminate, and PIGD subtypes. The assessed nonmotor features included global cognition, mood, and sleep. General cognition was assessed by the Mini-Mental State Examination and Montreal Cognitive Assessment (MoCA) [28]. To correct for the education effect, if the education period of PD patients was ≤12 years, the MoCA score (if < 30) was increased by 1 point. Depression and anxiety were measured using the Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale, respectively. The Parkinson Disease Sleep Scale (PDSS) was used to evaluate sleep. The Non-Motor Symptoms Questionnaire (NMSQuest) for PD was used to evaluate patients' NMSs and divided into nine domains, namely, cardiovascular, sleep, mood/cognitive, perception/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous [29,30].

Molecular analysis of *GBA* variants

To avoid sequencing the nearby *GBAP1*, the long-range polymerase chain reaction (LR-PCR) protocol was implemented with *GBA* gene-specific primers (F: AGGTCCCTGAGACAGATACTGG; R: CAATGAGACTTGAGGAAGGGCTC) and the TaKaRa LA Taq DNA Polymerase Hot-Start Version (Takara Bio) to amplify the entire *GBA* gene. An amplicon with a length of 11,246 base pairs (bp) was obtained. The cycling conditions for amplification were as

follows: initial denaturation at 94°C for 60 s, 30 cycles of denaturation at 98°C for 10 s, annealing at 68°C for 12 min, and extension at 72°C for 20 min. Lastly, samples were held at 4°C. After LR-PCR, the PCR products were fragmented using Hieff Smearase (YEASEN) to an average size of 150–250 bp before sequencing. Library preparation was performed using the Hieff NGS OnePot DNA Library Prep Kit for Illumina (YEASEN). Next generation sequencing (paired-end 150 bp) was then performed using a HiSeq 4000 sequencer (Illumina).

Based on whether they carried *GBA* variants, PD patients were divided into *GBA*-PD and NM-PD groups. Based on the criteria proposed by Petrucci et al. [23], the severity of *GBA* variants in the *GBA*-PD group was further classified into five classes: mild (causing nonneuropathic subtypes of Gaucher disease [GD] type 1, such as N370S), severe (known to cause neuropathic phenotypes of GD type 2 or 3, such as L444P), risk (related to risk factors of PD but not meaningful for GD, such as E326K and T369M), complex (two or more *GBA* variants, such as L444P-A456P-V460V), and unknown.

Statistical analysis

Descriptive statistics were calculated for demographic and clinical characteristics; continuous variables were reported as the mean and standard deviation, whereas categorical variables were reported as frequencies and proportions. For comparisons between the NM-PD and *GBA*-PD groups, linear regression analysis was used for continuous variables and logistic regression analysis was used for binary variables. Multinomial logistic regression with TD subtype as the comparator was performed to compare motor subtypes between the two groups. Probability values were two-tailed and calculated after adjusting for potential confounding factors, as listed in the tables. Furthermore, *GBA*-PD patients were divided into subgroups according to the severity of the *GBA* variant. Comparisons of demographic and clinical features among the mild, severe, and complex subgroups were performed using one-way analysis of variance, Kruskal–Wallis *H*-test, or Fisher exact test followed by post hoc analysis with Bonferroni adjustment. Results were deemed to be statistically significant if the *p*-value was <0.05. All statistical analyses were performed using IBM SPSS (v25.0).

RESULTS

Identified *GBA* variants

GBA gene sequencing was performed on 737 Chinese PD patients, 79 (*GBA*-PD, 10.72%) of whom carried 47 distinct *GBA* variants. The variant severity levels were eight (10.13%) mild, 28 (35.44%) severe, one (1.27%) risk, seven (8.86%) complex, and 35 (44.30%) unknown (Figure S1). Surprisingly, R163Q was the most common variant, with a cumulative frequency of 15.19% (12 cases, including 10 isolated cases and two cases as part of a recombinant allele). The second and third most common variants were L444P and R120W, with cumulative frequencies of 12.66% (10 cases, including seven isolated cases and three cases as part of a recombinant allele) and 7.59% (six isolated cases), respectively (Table S1).

Demographic and clinical features between *GBA*-PD and NM-PD groups

Of the 737 PD patients whose *GBA* gene was sequenced, demographic and clinical data were obtained for 673 patients. According to whether they carried *GBA* variants, these 673 PD patients were divided into *GBA*-PD ($n = 79$) and NM-PD ($n = 594$) groups. Of note, 32 of the 173 EOPD patients (18.50%) carried *GBA* variants.

The demographic, motor, and nonmotor characteristics of the *GBA*-PD and NM-PD groups are compared in Table 1. In terms of demographic data, there were no statistically significant differences in gender, formal education, disease duration, or LEDD between the two groups. However, patients with *GBA*-PD were younger (mean age = 57.2 years, SD = 9.7) compared with the NM-PD group (mean age = 61.2 years, SD = 9.6), had a significantly earlier age at onset (mean = 53.3 years, SD = 9.7) compared with the NM-PD group (mean = 57.1 years, SD = 10.1), and had higher prevalence of EOPD (40.5%) compared with the NM-PD group (23.9%), when adjusting for gender and disease duration ($p = 0.001$). In addition, patients with *GBA*-PD had a higher frequency of family history of PD (13.9%) compared with the NM-PD group (5.7%), when adjusting for age, gender, and disease duration ($p = 0.014$). With respect to motor characteristics, the prevalence of the PIGD subtype, which reflects more axial symptoms and less tremor, was not significantly different between the NM-PD and *GBA*-PD groups; this subtype was the most common phenotype in both groups. However, patients with *GBA*-PD had more severe UPDRS ADL scores, UPDRS motor scores, and modified H-Y stages compared with the NM-PD group. Regarding the NMSs, there were no significant group differences in cognitive impairment. However, depression, anxiety, and sleep impairments were more prevalent in the *GBA*-PD group than the NM-PD group.

Demographic and clinical features among *GBA*-PD subgroups

Considering there was only one *GBA*-PD patient in the risk group, we compared demographic and clinical data among the mild, severe, and complex subgroups (Table 2). Among the demographic and motor features, the only significant subgroup difference emerged for UPDRS motor scores. In the post hoc analysis, *GBA*-PD patients in the severe subgroup had more severe UPDRS motor scores than those in the mild subgroup. Regarding scores linked to NMSs, HAMD, PDSS, and NMSQuest scores were significantly different among the three subgroups. Post hoc analysis revealed that *GBA*-PD patients in the complex and severe subgroups had more severe HAMD and NMSQuest scores than those in the mild subgroup. In addition,

TABLE 1 Comparison of demographic and clinical characteristics between *GBA*-PD and NM-PD patients

Variable	*GBA*-PD, *n* = 79	NM-PD, *n* = 594	*p*[a]
Age, years	57.2 ± 9.7	61.2 ± 9.6	0.001[b]*
Gender, male, *n* (%)	41 (51.9)	330 (55.6)	0.471[c]
Formal education, years	9.3 ± 4.1	10.2 ± 4.1	0.073
Age at onset, years	53.3 ± 9.7	57.1 ± 10.1	0.001[b]*
EOPD, *n* (%)	32 (40.5)	142 (23.9)	0.001[b]*
Family history of PD, *n* (%)	11 (13.9)	34 (5.7)	0.014*
Disease duration, years	3.9 ± 3.1	4.2 ± 3.9	0.728[d]
LEDD, mg/day	405.7 ± 309.4	375.2 ± 330.3	0.077
UPDRS ADL score	11.8 ± 6.6	10.3 ± 6.0	0.001*
UPDRS motor score	30.0 ± 16.5	24.9 ± 14.2	<0.001[e]*
H-Y stage	2.5 ± 1.2	1.9 ± 0.8	<0.001*
Motor subtype, *n* (%)			
TD	20 (25.3)	138 (23.2)	
PIGD	44 (55.7)	355 (59.8)	0.712
Indeterminate	15 (19.0)	101 (17.0)	0.889
MMSE score	26.4 ± 3.7	26.7 ± 3.7	0.402[f]
MoCA score	22.6 ± 4.9	22.6 ± 4.9	0.893[f]
HAMD score	12.8 ± 9.1	10.3 ± 7.4	0.004*
HAMA score	10.2 ± 8.1	7.5 ± 7.2	0.001*
PDSS score	103.5 ± 32.4	116.3 ± 23.0	<0.001*
NMSQuest score	11.3 ± 6.3	9.0 ± 4.9	<0.001*

Note: Data are reported as mean ± SD or *n* (%). Probability values were calculated using linear regression or logistic regression.

Abbreviations: ADL, activities of daily living; EOPD, early onset PD; *GBA*-PD, *GBA*-related PD; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; H-Y, Hoehn-Yahr; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NM-PD, non-*GBA*-mutated PD; NMSQuest, Non-Motor Symptoms Questionnaire; PD, Parkinson disease; PDSS, Parkinson Disease Sleep Scale; PIGD, postural instability gait difficulty; TD, tremor-dominant; UPDRS, Unified Parkinson's Disease Rating Scale.

*$p < 0.05$.

[a]Adjusted for age, gender, and disease duration (unless otherwise indicated).

[b]Adjusted for gender and disease duration.

[c]Adjusted for age and disease duration.

[d]Adjusted for age and gender.

[e]Adjusted for age, gender, disease duration, and LEDD.

[f]Adjusted for age, gender, disease duration, and years of formal education.

GBA-PD patients in the complex subgroup had higher PDSS scores than those in the mild subgroup.

NMSs based on NMSQuest

Because there were significant differences in NMSQuest scores between the *GBA*-PD and NM-PD groups, and among the mild, severe, and complex subgroups, the frequency of the nine domains in NMSQuest were further compared (Figure 1). Patients with *GBA*-PD had a higher prevalence of sleep, mood/cognitive, perception/hallucinations, gastrointestinal, urinary, sexual function, and miscellaneous symptoms compared to the NM-PD group, adjusting for age, gender, and disease duration (Table S2). Among the subgroups, *GBA*-PD patients in the complex and severe subgroups had a higher prevalence of mood/cognitive and gastrointestinal symptoms compared with the mild subgroup. Additionally, *GBA*-PD patients carrying severe variants had a higher prevalence of miscellaneous domain symptoms than *GBA*-PD patients carrying mild variants (Table S3).

DISCUSSION

To our knowledge, this is the first comprehensive analysis of the entire *GBA* gene in a large cohort of Chinese PD patients. We detected *GBA* variants in 79 (10.72%) patients. For the results of the genotype–phenotype correlations, *GBA*-PD patients had an approximately 4 year earlier age at onset and more severe motor

TABLE 2 Comparison of demographic and clinical characteristics among *GBA*-related PD patients grouped by *GBA* variant classes

Variable	Mild, *n* = 8	Severe, *n* = 28	Complex, *n* = 7	*p*	Post hoc
Age, years	58.9 ± 9.8	55.5 ± 10.2	51.0 ± 6.2	0.299	
Gender, male, *n* (%)	4 (50.0)	18 (64.3)	3 (42.9)	0.540	
Formal education, years	9.0 ± 2.4	10.0 ± 3.8	10.6 ± 1.8	0.589	
Age at onset, years	55.3 ± 8.8	51.0 ± 10.1	47.7 ± 7.1	0.308	
EOPD, *n* (%)	3 (37.5)	15 (53.6)	5 (71.4)	0.545	
Family history of PD, *n* (%)	1 (12.5)	3 (10.7)	2 (28.6)	0.527	
Disease duration, years	3.6 ± 2.7	4.5 ± 3.5	3.3 ± 2.1	0.574	
LEDD, mg/day	407.1 ± 274.6	469.9 ± 349.4	439.3 ± 379.9	0.895	
UPDRS ADL score	8.5 ± 4.2	12.6 ± 6.6	12.1 ± 8.2	0.307	
UPDRS motor score	17.6 ± 6.1	34.5 ± 15.7	31.4 ± 22.0	0.036*	0.032[a]*
H-Y stage	1.8 ± 0.6	2.8 ± 1.3	2.6 ± 1.7	0.104	
MMSE score	26.8 ± 3.3	27.2 ± 2.1	27.4 ± 1.5	0.993	
MoCA score	22.8 ± 4.6	23.7 ± 3.6	22.7 ± 3.9	0.725	
HAMD score	6.1 ± 5.7	15.0 ± 9.3	17.7 ± 8.1	0.022*	0.042[a]*, 0.038[b]*
HAMA score	8.9 ± 4.5	11.0 ± 8.2	12.7 ± 8.8	0.724	
PDSS score	121.3 ± 21.1	102.4 ± 31.4	76.9 ± 48.3	0.044*	0.039[b]*
NMSQuest score	6.3 ± 5.2	12.0 ± 5.8	14.3 ± 5.1	0.018*	0.045*, 0.025[b]*

Note: Data are reported as mean ± SD or n (%). Group comparisons were calculated using analysis of variance, Kruskal–Wallis *H*-test, or Fisher exact test followed by post hoc analysis with Bonferroni adjustment.

Abbreviations: ADL, activities of daily living; EOPD, early onset PD; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; H-Y, Hoehn-Yahr; LEDD, levodopa equivalent daily dose; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NMSQuest, Non-Motor Symptoms Questionnaire; PD, Parkinson disease; PDSS, Parkinson Disease Sleep Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

*$p < 0.05$.

[a]Statistically significant difference between the mild and severe subgroups.

[b]Statistically significant difference between the mild and complex subgroups.

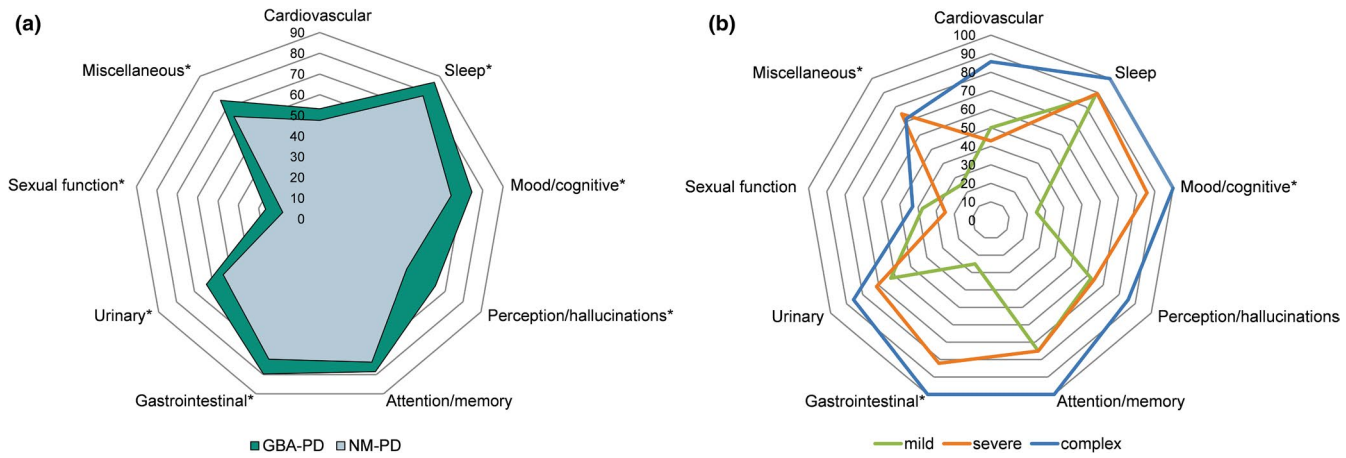

FIGURE 1 Comparison of frequency of NMSs classified by domain among different patient groups. (a) Frequency (%) of the nine domains of NMSs in *GBA*-PD versus NM-PD groups. (b) Frequency (%) of the nine domains of NMSs among *GBA*-PD subgroups carrying mild, severe, and complex variants. *$p < 0.05$. Statistical comparisons are shown in Tables S2 and S3. Abbreviations: *GBA*-PD, *GBA*-related PD; NM-PD, non-*GBA*-mutated PD; NMSs, nonmotor symptoms; PD, Parkinson disease [Colour figure can be viewed at wileyonlinelibrary.com]

and nonmotor characteristics than NM-PD patients. Furthermore, among the three *GBA*-PD subgroups, patients carrying severe and complex variants had a higher burden of NMSs, especially depression, and more prevalent mood/cognitive and gastrointestinal symptoms than patients carrying mild variants. Therefore, the effect of *GBA* variant status on phenotypic profile seems to depend on the severity, and complex variants and severe variants may underlie similar phenotypes.

In our cohort, 10.72% of PD patients carried one or more variants in the *GBA* gene. This is much higher than the *GBA* variant rate (3.64%) in the Chinese population estimated in a previous meta-analysis [31], which may be attributed to previous studies in the Chinese population focusing on detecting relatively common *GBA* variants, such as L444P and R120W [32,33]. Notably, the detected frequency is slightly higher than the *GBA* variant rate (8.7%) in 187 Chinese PD patients with sequencing of the entire *GBA* gene [12], which may be due to the large difference in sample size. Surprisingly, R163Q was the most common *GBA* variant (1.63%) among the 737 patients with PD in this study. Because R163Q is a relatively common variant (0.3%) in healthy Asian populations according to the Genome Aggregation Database, it is currently difficult to correctly classify the severity of the R163Q variant in *GBA*-PD patients. However, carrying the R163Q variant may still be a risk factor for PD. Therefore, it is necessary to increase knowledge about *GBA* variants that are common in healthy Asian populations and to accumulate information about *GBA* variants other than L444P and R120W. After R163Q, L444P was the most common (1.36%) pathogenic *GBA* variant identified in PD patients in this study, which is consistent with the results of a previous study in China [31]. Thus, this finding supports the view of L444P as a common pan-racial variant.

The prevalence of *GBA* variants in EOPD patients (age at onset ≤ 50 years) rose to 18.50% in the present study, which is in line with previous reports [23,34,35]. Recently, several studies have performed whole-exome sequencing of EOPD patients in the Chinese population to better understand the clinical and genetic correlations of *GBA*, *SNCA*, and *LRRK2* in EOPD [11,36], indicating that *GBA* screening in Chinese EOPD patients is important for diagnosis.

Compared with NM-PD cases, *GBA*-PD patients in the present study were approximately 4 years younger at the onset of symptoms. This finding is similar to results reported by studies from North America and the United Kingdom [19,37] as well as a previous meta-analysis of the Chinese population [38]. However, a study from Germany reported that the age at onset of *GBA*-PD could be as much as 6 years earlier compared with NM-PD [17].

We confirmed the significant association of *GBA* variants with more severe motor symptoms and NMSs (specifically depression, anxiety, and sleep disorders), which was mainly due to the correlation between the extent of Lewy body pathology and clinical symptoms. Autopsy pathology has revealed that *GBA*-PD patients tend to have more diffuse and widespread neocortical Lewy body-type pathology compared to NM-PD patients [9]. In addition, experimental data have shown that, mechanistically, GCase and α-syn form a bidirectional pathogenic loop [39]: (i) the functional loss of GCase caused by *GBA* variant compromises the degradation of lysosomal α-syn, leading to accumulation of α-syn; and (ii) aggregated α-syn itself inhibits the lysosomal activity of GCase. Consequently, *GBA*-PD patients satisfy the two conditions of this bidirectional pathogenic loop in parallel, thereby forming an autoreinforcement mechanism. However, the relationship between the severity of *GBA* variant and the level of GCase activity has not been clearly elucidated due to the limited number of *GBA*-PD patients carrying variants of varying severity [23,40]. Therefore, clinical data of patients with different severity of *GBA* variants are still needed for detailed comparison.

This study demonstrated that *GBA*-PD patients with complex and severe classes had more severe NMSs compared with patients with mild variants, which is mostly consistent with the results of previous studies [15,23]. Importantly, this study provides the first evidence that the existence of depression in PD is variant-specific. A recent study within the *GBA*-PD subgroups focused on psychiatric symptoms, including hallucinations, delusions, and impulsive–compulsive behavior, but ignored depression [23]. Lastly, considering the nine domains of NMSs, the frequencies of mood/cognitive and gastrointestinal domain symptoms in the complex and severe subgroups were higher than those in the mild subgroup. Therefore, the clinical features of NMSs in *GBA*-PD patients seem to be influenced by the severity of *GBA* variants. Importantly, our clinical data support the view that complex variants are similar to severe variants, which is consistent with a recent review [41].

The strengths of the present study are as follows: (i) the establishment of a relatively large *GBA*-PD cohort in the Chinese population for meaningful epidemiological comparisons; (ii) screening of the entire *GBA* gene and avoidance of *GBAP1* interference, which makes the variant-specific analysis more accurate; and (iii) the support of complex variants and severe variants to share similar phenotypic profiles, according to clinical data.

The present study is also subject to several limitations. (i) In *GBA*-PD patients, the limited number of subjects carrying variants of varying severity may mask additional significant differences. (ii) Considering the heterogeneity of the cohort, we recommend that these findings are explored in de novo *GBA*-PD cohorts and, ideally, in cohorts of *GBA* nonmanifesting carriers. (iii) All patients with idiopathic PD in this study underwent *GBA* gene testing, but this does not rule out the possibility that some PD patients have common PD pathogenic genes, such as *SNCA* and *LRRK2*, which may have impacted the results. (iv) We unfortunately did not test the onset and longitudinal evolution of motor complications (motor fluctuations and dyskinesia) and key NMSs (such as cognitive impairment and hallucinations), which will be important in future research.

In conclusion, the prevalence of *GBA*-PD patients in the Chinese population is very high, which contributes to the large proportion of EOPD cases. Our study has expanded the spectrum of nonmotor characteristics in *GBA*-PD patients and indicates that variant severity may underlie different phenotypic features. Notably, the severe and complex groups seem to have similar phenotypes. In this context, stratifying PD patients based on the severity of *GBA* variants should become a necessary prerequisite for selecting specific treatments.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

Jingru Ren: Conceptualization (lead), data curation (equal), formal analysis (lead), investigation (equal), methodology (equal), validation (equal), writing–original draft (lead), writing–review & editing (equal). **Ronggui Zhang:** Conceptualization (equal), formal analysis (equal), investigation (equal), validation (equal), visualization (equal). **Chenxi Pan:** Methodology (equal), supervision (equal), validation (equal), visualization (equal), writing–review & editing (equal). **Jianxia Xu:** Data curation (equal), formal analysis (equal), methodology (equal), supervision (equal), validation (equal). **Haochen Sun:** Data curation (equal), formal analysis (equal), supervision (equal), writing–review & editing (equal). **Ping Hua:** Supervision (equal), validation (equal), visualization (equal), writing–review & editing (equal). **Li Zhang:** Supervision (equal), validation (equal), visualization (equal), writing–review & editing (equal). **Wenbin Zhang:** Formal analysis (equal), methodology (equal), validation (equal), visualization (equal), writing–review & editing (equal). **Pingyi Xu:** Supervision (equal), validation (equal), visualization (equal), writing–review & editing (equal). **Changyan Ma:** Methodology (equal), supervision (equal), validation (equal), writing–review & editing (equal). **Weiguo Liu:** Conceptualization (equal), funding acquisition (lead), investigation (equal), methodology (equal), project administration (equal), supervision (lead), validation (lead), writing–review & editing (equal).

DATA AVAILABILITY STATEMENT

The original data for this study can be obtained from the corresponding author via email upon reasonable request.

ORCID

Jingru Ren https://orcid.org/0000-0002-9186-6621
Weiguo Liu https://orcid.org/0000-0001-5916-9837

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Supplementary material

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