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Supporting Data

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GBA-Related Parkinson's Disease: Dissection of Genotype–Phenotype Correlates in a Large Italian Cohort

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ABSTRACT: Background: Variants in *GBA* are the most common genetic risk factor for Parkinson's disease (PD). The impact of different variants on the PD clinical spectrum is still unclear.

Objectives: We determined the frequency of *GBA*-related PD in Italy and correlated *GBA* variants with motor and nonmotor features and their occurrence over time.

Methods: Sanger sequencing of the whole *GBA* gene was performed. Variants were classified as mild, severe, complex, and risk. β -glucocerebrosidase activity was measured. The Kaplan-Meier method and Cox proportional hazard regression models were performed.

Results: Among 874 patients with PD, 36 variants were detected in 14.3%, including 20.4% early onset. Patients with *GBA*-PD had earlier and more frequent occurrence of several nonmotor symptoms. Patients with severe and complex *GBA*-PD had the highest burden of symptoms and a higher risk of hallucinations and cognitive impairment. Complex *GBA*-PD had the lowest β -glucocerebrosidase activity.

Conclusions: *GBA*-PD is highly prevalent in Italy. Different types of mutations underlie distinct phenotypic profiles. © 2020 International Parkinson and Movement Disorder Society

Key Words: dementia; *GBA*; genotype–phenotype correlates; impulsive–compulsive behavior; Parkinson's disease

Heterozygous variants in the *GBA* gene, encoding the lysosomal enzyme β -glucocerebrosidase (GCase), are the most common genetic risk factor for Parkinson's disease (PD) worldwide.¹⁻⁵

Overall, 5% to 10% of patients with PD carry a heterozygous *GBA* variant, but such frequency varies widely among populations, from 10% to 31% in Ashkenazi Jewish to 3% to 12% in non-Jewish cohorts, and 2.8% to 4.5% in Italy.⁵⁻¹¹ However, most studies have only tested the most common *GBA* mutations, likely underestimating prevalence rates. To date, more than 500 pathogenic variants have been reported and classified as complex, severe, and mild based on the mutation type and residual GCase activity in patients with Gaucher disease (GD).^{5,12,13} Other variants not associated to GD recently emerged as risk factors for PD.¹⁴⁻¹⁷

GBA-PD is overall characterized by earlier onset, worse motor impairment, higher risk of cognitive decline and depression, more rapid progression, and decreased survival.^{3,7,10} Few studies have attempted to link variant severity with some clinical features,¹⁸⁻²¹ yet genotype-phenotype correlates have not been fully elucidated.

Here, we screened the whole *GBA* gene in a large cohort of Italian patients with PD and measured GCase activity in a subgroup. We performed a detailed comparison of motor and nonmotor features, and their occurrence over time, in patients with and without *GBA* mutations and, within the *GBA* group, among patients carrying variants of different severity.

Patients and Methods

We recruited 874 unrelated PD probands from 13 neurological tertiary centers spread in the Italian territory. Approval was obtained by the Institutional Ethics Committee of the Coordinator Center (Protocol: 11799/08) and confirmed by the committees of each participating center. Written informed consent was obtained. The whole *GBA* coding region was sequenced, and variants were divided into 5 classes: mild (known to cause nonneuronopathic GD), severe (causing neuronopathic GD), risk (associated with higher PD risk, but not reported in GD), complex (2 or more variants in *cis* as the result of conversion, fusion, insertion of parts of *GBAP1* into *GBA*), and unknown. GCase activity was assessed in a subset of patients.

Methodological details regarding inclusion criteria, clinical assessment, molecular analysis, measurement of GCase enzymatic activity, and statistical analysis are reported in the Supplementary Material.

Results

Sequencing of the *GBA* gene was carried out in 874 patients with PD, and clinical data were obtained for 850 of them. Genetic variants were identified in 125 subjects (*GBA*-PD, 14.3%), including 36/176 (20.4%) early-onset PD (EOPD) and 89/674 (13.2%) late-onset PD cases. Details of all identified variants are presented

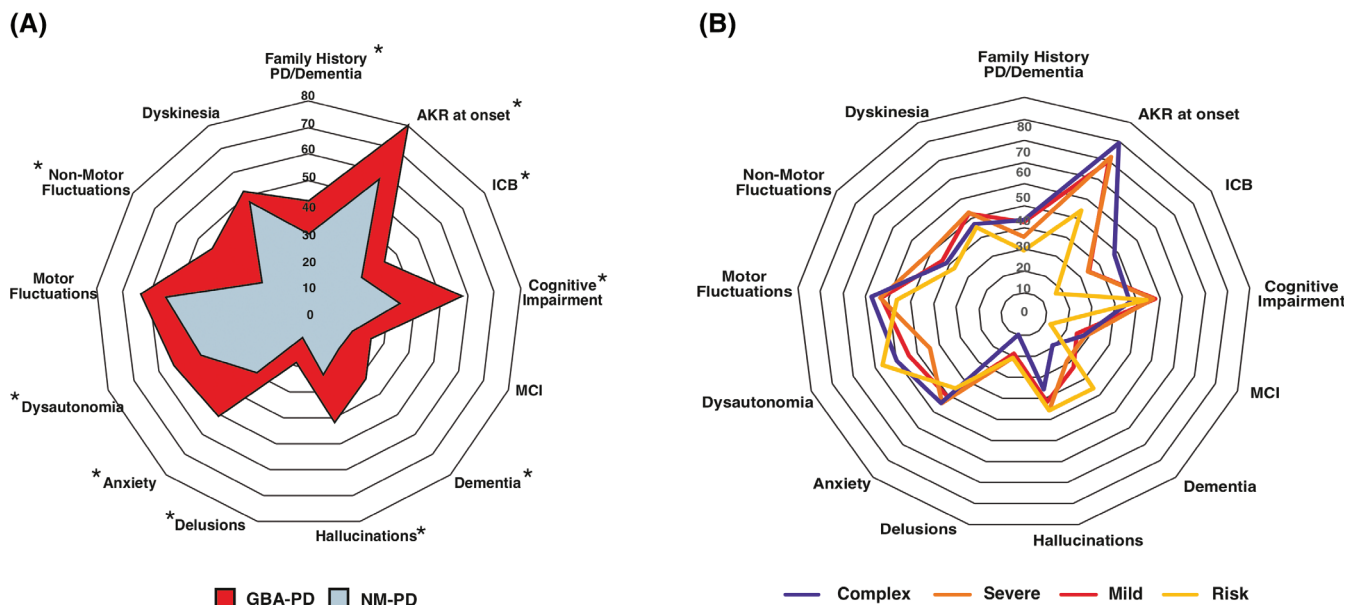


FIG. 1. Comparison of frequency of motor and nonmotor symptoms among different groups. (A) Frequency (%) of motor and nonmotor symptoms in *GBA*-PD versus NM-PD. (B) Frequency (%) of motor and nonmotor symptoms among *GBA*-PD subgroups carrying mild, complex, severe, and risk variants. Statistical comparisons are reported in Supplementary Table 5. *Significantly different comparisons (for details, see Supplementary Table 3). AKR, akinetic-rigid phenotype; *GBA*-PD, *GBA*-mutated PD; ICB, impulsive compulsive behavior; MCI, mild cognitive impairment; NM-PD, nonmutated PD; PD, Parkinson's disease.

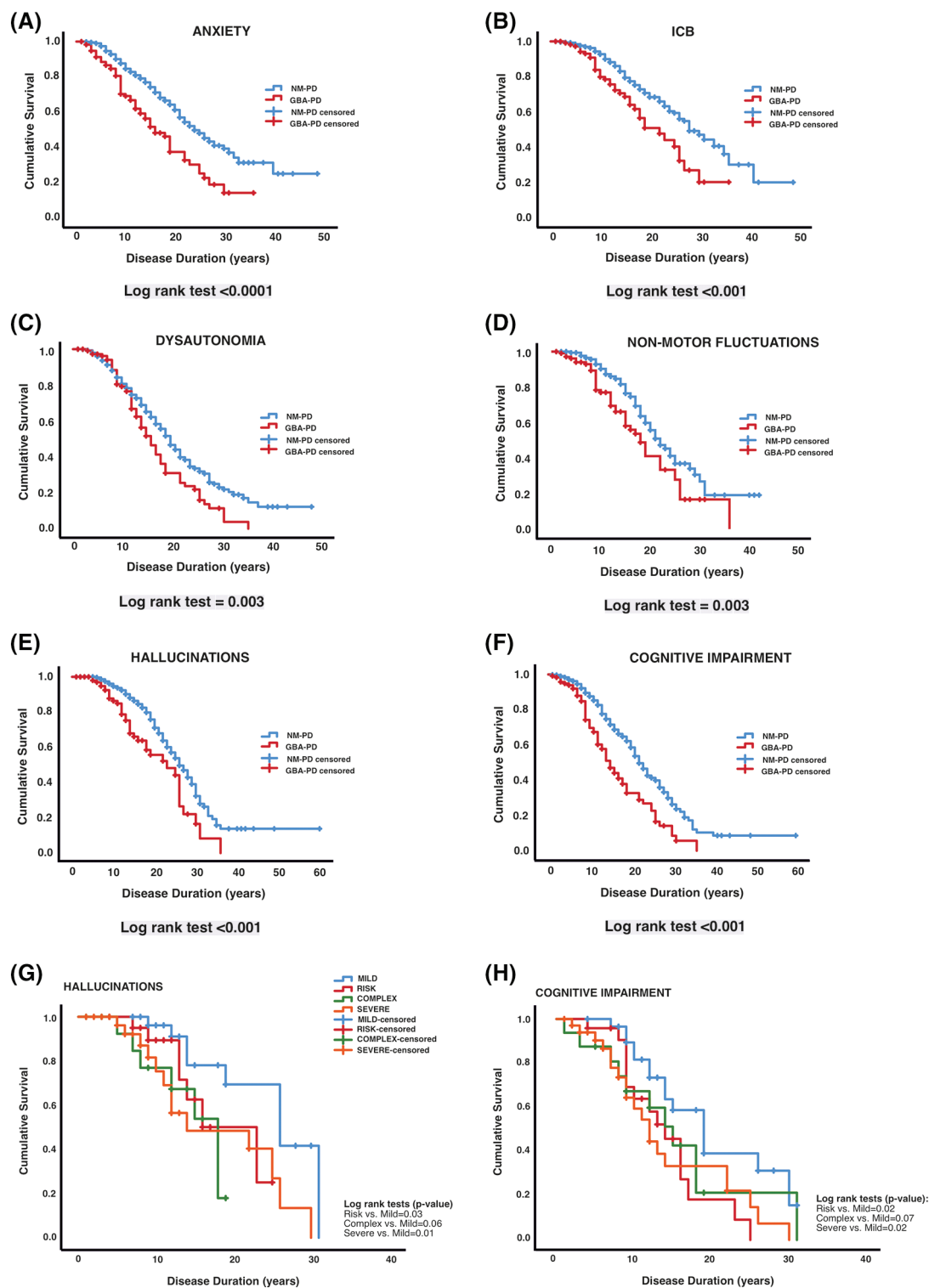


FIG. 2. Comparison of survival curves in GBA-PD versus NM-PD, and in carriers of distinct types of *GBA* variants. Kaplan-Meier method for disease-duration scale time and log-rank tests were used for comparison of survival curves in GBA-PD versus NM-PD (**A–F**) and in GBA carriers of mild, complex, severe, and risk variants (**G–H**). Log-rank tests showed that GBA-PD developed anxiety, ICB, dysautonomia, nonmotor fluctuations, hallucinations, delusions (not shown in figure; $P < 0.001$), and cognitive impairment significantly earlier than NM-PD. Log-rank tests also showed that patients with severe and risk *GBA* variants manifested hallucinations and cognitive impairment earlier than carriers of mild *GBA* variants. Patients with complex *GBA* variants had earlier hallucinations and cognitive impairment than carriers of mild *GBA* variants, albeit not significantly. GBA-PD, GBA-mutated PD; ICB, impulsive compulsive behavior; MCI, mild cognitive impairment; NM-PD, nonmutated PD; PD, Parkinson's disease.

in the Supplementary Results and Supplementary Tables 1 and 2.

Normalized GCase activity was calculated in 38 patients with GBA-PD, 27 nonmutated PD patients (NM-PD), 3 patients with GD, and 21 healthy controls. The patients with GD had the lowest GCase activity, followed by GBA-PD and NM-PD ($P = 0.0001$). When GBA-PD patients were stratified by mutation type, GCase activity was significantly lower in carriers of complex variants compared with other categories (Supplementary Fig. 1).

Clinical features comparing GBA-PD and NM-PD groups are reported in Figure 1 and Supplementary Table 3. Compared with NM-PD the patients with GBA-PD showed a significantly younger age and more common akinetic-rigid phenotype at onset; more frequent family history for PD; and a higher burden of all non-motor features, including anxiety, impulsive-compulsive behavior (ICB), dysautonomia, hallucinations, delusions, cognitive impairment, and nonmotor fluctuations. The frequency of motor complications (motor fluctuations and dyskinesia) was comparable in the 2 groups, albeit occurring earlier in patients with GBA-PD. Hallucinations also manifested earlier in the GBA-PD group, who was overall exposed to a lower total levodopa equivalent daily dose (LEDD) but a similar dose of Dag.

The patients with GBA-PD had a significantly higher risk of having a more advanced disease stage (Hoehn and Yahr >2), even after adjusting for age and gender. There was no difference in terms of risk of motor fluctuations and dyskinesia. This group also had a significantly higher risk of anxiety, ICB, dysautonomia, hallucinations, and cognitive impairment as well as nonmotor fluctuations, even after adjusting for gender, age, total LEDD, and LEDD Dag (Supplementary Tables 4 and 5). Log-rank tests showed that all these features also developed earlier in the GBA-PD group than in the NM-PD group (Fig. 2).

The patients with GBA-PD were further divided into 4 groups according to the type of *GBA* variant: mild (mGBA-PD), complex (cGBA-PD), severe (sGBA-PD), or risk alleles. No differences emerged among the groups in the frequency of motor and nonmotor symptoms except for ICB, delusions, and dementia (Supplementary Table 6).

In the Cox proportional hazard model, patients with mGBA-PD had a lower risk of dyskinesia than patients with sGBA-PD, even after adjusting for age, gender, and total and Dag LEDD. The patients with mGBA-PD also had a lower risk of hallucinations and cognitive impairment than the other 3 groups (not reaching statistical significance for comparison with cGBA-PD), which survived all adjustments. The risk of delusions was lower in patients with mGBA-PD compared with cGBA-PD and sGBA-PD groups, and survived all adjustments. There were no significant differences among *GBA* groups for anxiety, ICB, dysautonomia, and nonmotor fluctuations (Supplementary Table 7).

Log-rank tests showed that patients with mGBA-PD had a significantly later occurrence of cognitive impairment and hallucinations (compared with sGBA-PD and risk GBA-PD groups; Fig. 2) and delusions (compared with sGBA-PD and cGBA-PD groups). There were no differences among groups with regard to the onset of anxiety ($P = 0.4$), ICB ($P = 0.3$), dysautonomia ($P = 0.3$), motor fluctuations ($P = 0.2$), nonmotor fluctuations ($P = 0.2$), and dyskinesia ($P = 0.1$).

Discussion

Here we report the first comprehensive analysis of the whole *GBA* gene in 874 Italian patients with PD. We detected *GBA* variants in 125 (14.3%) subjects, well above the 7% to 10% frequency reported in non-Ashkenazi Jewish populations.^{1,6,22-28}

Previous screenings in 2 other Italian PD cohorts disclosed a frequency of 3% to 5%.⁸⁻¹⁰ However, these studies focused either on detecting the 2 most common mutations (N370S and L444P) or on sequencing exons 9 and 10 only. Conversely, we detected 36 distinct variants, of which 3 novel. The N370S and L444P mutations were found in only 47%, and mutations in exons 9 and 10 in only 58% of the positive cases. These findings underlie the following 2 important concepts: (1) the frequency of *GBA*-related PD in Italy is among the highest worldwide among non-Ashkenazi Jewish populations and (2) a focused mutational screening cannot represent the method of choice at least in the Italian population.

Consistent with previous studies,^{16,29} the prevalence of *GBA* mutations among EOPD patients raised to 20.3%, suggesting that *GBA* screening in EOPD is as relevant for diagnostic purposes as testing the most common EOPD genes, such as *PARK2* and *PINK1* or even *LRRK2*.

We observed significant differences of normalized GCase values in the GBA-PD group versus both healthy controls and NM-PD groups, as reported.³⁰ When comparing enzymatic activity among different mutation classes, complex variants had the lowest activity, whereas risk variants had the highest. These data require replication in larger cohorts and correlation with clinical data given the variability at the individual level.

We confirm a significant association of *GBA* variants with earlier age at onset, positive family history for PD, and more rapid disease progression.^{5,7,10}

As a novel finding, we show a significant association of GBA-PD with akinetic-rigid onset and several non-motor symptoms, such as anxiety, ICB, hallucinations, and dysautonomia, which also occurred earlier. This was paralleled by a significantly lower dopaminergic daily dose, supporting the neuropsychiatric and autonomic vulnerability of this group of patients. The increased predisposition to develop ICB, previously

reported in *PARK2*-associated PD,³¹ supports the view that ICB may represent a manifestation of PD rather than a pure drug-induced phenomenon. Dysautonomia also tended to occur earlier in patients with *GBA*. Indeed, worse autonomic and cognitive functions in *de novo* PD predict the development of ICB during the disease course,³² suggesting a close link of these symptoms as predictors of disease deterioration.

Although the clinical spectrum of *GBA*-PD seems well delineated, the variability of clinical features among mutation carriers is remarkable. This may be at least partly explained by the diverse impact of distinct *GBA* mutations. To date, only a few studies have attempted to delineate the phenotypic profile associated to specific mutation classes, showing earlier age at onset and a greater risk for dementia and other nonmotor symptoms in carriers of severe variants.^{10,18-21} In the present study, we further addressed this issue by dividing patients with *GBA*-PD into subgroups based on the variant type and attempted to profile the clinical features that recurred more frequently, or earlier in the disease course, within each subgroup. Severe *GBA* variants were characterized by younger onset and more severe progression as per the shorter time to develop balance disturbances and the higher risk of hallucinations and cognitive impairment. Subjects carrying complex variants had a similar phenotype, with a comparable risk of hallucinations and dementia, but also a higher frequency of delusions. Carriers of mild variants showed a milder phenotype, reaching postural instability after longer time, less frequent delusions, and later cognitive impairment. Finally, patients carrying a risk allele had the highest age at PD onset and were the only patients showing tremor-dominant phenotype at onset and later occurrence of nonmotor fluctuations. When considering ICB in the 4 subgroups, risk and mild variant carriers had, respectively, the lowest and highest frequency, likely determined by having the lowest and highest dose of Dag. This might reflect a lower vulnerability to late psychiatric complications (hallucinations and delusions) of mild variant carriers who could be treated with higher concentrations of Dag.

The main limitation of this study relates to its retrospective design. We tried to minimize this by employing the Kaplan-Meier method for the disease-duration scale time and log-rank tests for the comparison of survival curves. Moreover, we acknowledge the lack of objective outcome measures to assess symptom severity. Yet, given the heterogeneity of the cohort (including patients with widely variable disease duration and assessed in different pharmacological conditions), a comparison of scores would have provided unreliable results.

This study has a number of strengths. First, it provides a comprehensive assessment of motor and non-motor features in the same large cohort of subjects, showing previously unreported associations. Second, it reports for the first time a comparison among all

mutation classes, including complex alleles. Albeit these are considered similar to severe variants, our clinical and enzymatic data support the view that complex variants represent a distinct group. Finally, it is worth reporting the full picture of *GBA*-related PD in a different population from those described so far to allow meaningful epidemiological comparisons.

In conclusion, *GBA*-related PD has a high prevalence in the Italian population, also contributing to a significant proportion of EOPD cases. Our data expand the spectrum of nonmotor features associated to *GBA* and suggest that different types of mutations might underlie distinct phenotypic profiles. This evidence does not merely carry a clinical implication, but it is relevant in the attempt of developing disease-modifying strategies.³³ A fundamental research question now is whether *GBA* phenotypes related to distinct mutation types have a different rate of disease progression and survival in a prospective cohort. If so, stratification by mutation type will be mandatory when designing a clinical trial focusing on *GBA*-PD. ■

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Appendix

Other collaborators of the ITA-GENE-PD Study Group are: Maria Concetta Altavista (RM), Marianna Amboni (NA), Gianluca Ardolino (MI), Alfredo Berardelli (RM), Filippo Cogiamanian (MI), Carlo Colosimo (TR), Danilo Costanti (TR), Giuseppe De Michele (NA), Carlo Di Bonaventura (RM), Giulia Di Lazzaro (RM), Vincenzo Di Lazzaro (RM), Antonio Emanuele Elia (MI), Roberto Erro (SA), Gina Ferrazzano (RM), Andrea Guerra (RM), Tamara Ialongo (RM), Maria Chiara Malaguti (TN), Marta Melis (CA), Elena Moro (Grenoble), Valentina Oppo (CA), Donatella Ottaviani (TN), Silvio Peluso (NA), Maria Luisa Quadri (Rotterdam), Luigi Michele Romito (MI), Marianna Sarchioto (London, TO), Tommaso Schirinzi (RM), Chiara Sorbera (ME), Alessandro Stefani (RM), Astrid Thomas (CH), Maria Luisa Valente (PV), and Giampiero Volpe (SA). ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Penetrance of Glucocerebrosidase (GBA) Mutations in Parkinson's Disease: A Kin Cohort Study

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