# GBA-related Parkinson disease: dissection of genotype-phenotype correlates in a large Italian cohort

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# Abstract

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

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

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

**Results:** Among 874 PD patients, 36 variants were detected in 14.3%, including 20.4% early onset. GBA-PD had earlier and more frequent occurrence of several non-motor symptoms. Severe and complex GBA-PD had the highest burden of symptoms and 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.

# Introduction

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

Overall, 5-10% PD carry a heterozygous *GBA* variant, but such frequency varies widely among populations, from 10-31% in Ashkenazi Jewish (AJ) to 3-12% in non-Jewish cohorts, and 2.8-4.5% in Italy.5-11 However, most studies have only tested the commonest *GBA* mutations, likely underestimating prevalence rates. To date, over 500 pathogenic variants have been reported, being 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 PD subjects, and measured GCase activity in a subgroup. We performed a detailed comparison of motor and non-motor 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 thirteen neurological tertiary centers spread on the Italian territory. Approval was obtained by the Institutional Ethics Committee of the Coordinator Centre (Pr. 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 five classes: mild (known to cause non-neuronopathic GD); severe (causing neuronopathic GD); risk (associated to higher PD risk but not reported in GD); complex (two or more variants *in cis* as the result of conversion, fusion, insertion of parts of *GBAP1* into *GBA)*; 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 Supplementary Material.

# Results

Sequencing of the *GBA* gene was carried out in 874 PD patients, and for 850 of them clinical data were obtained. Genetic variants were identified in 125 subjects (GBA-PD, 14.3%), including 36/176 (20.4%) EOPD and 89/674 (13.2%) late-onset PD cases. Details of all identified variants are presented in Supplementary Results and Supplementary Tables 1 and 2.

Normalized GCase activity was calculated in 38 GBA-PD, 27 non-mutated PD patients (NM-PD), 3 GD subjects and 21 healthy controls (HC). GD had the lowest GCase activity, followed by GBA-PD and NM-PD (p = 0.0001). When GBA subjects were stratified by mutation type, GCase activity was significantly lower in carriers of complex variants compared to other categories (Supplementary Figure 1).

Clinical features comparing GBA-PD vs NM-PD are reported in Figure 1 and Supplementary Table 3. Compared to NM-PD, GBA-PD showed a significantly younger age and commoner akinetic-rigid phenotype at onset, a 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 non-motor fluctuations. The frequency of motor complications (motor fluctuations and dyskinesia) was comparable in the two groups, albeit occurring earlier in GBA-PD. Hallucinations also manifested earlier in GBA-PD subjects, who were overall exposed to a lower total LEDD but a similar dose of Dag.

GBA-PD had a significantly higher risk of having more advanced disease stage (Hoehn & Yahr, H&Y>2), even after adjusting for age and gender. There was no difference in terms of risk of motor fluctuations and dyskinesia. GBA-PD also had a significantly higher risk of anxiety, ICB, dysautonomia, hallucinations and cognitive impairment, as well as non-motor 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 GBA-PD than in NM-PD (Figure 2).

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

At Cox Proportional Hazard Model, mGBA had a lower risk of dyskinesia than sGBA, even after adjusting for age, gender, total and Dag LEDD. mGBA also had a lower risk of hallucinations and cognitive impairment than the other three groups (not reaching statistical significance for comparison with cGBA), which survived all adjustments. Risk of delusions was lower in mGBA compared to cGBA and sGBA and survived all adjustments. There were no significant differences among GBA groups for anxiety, ICB, dysautonomia and non-motor fluctuations (Supplementary Table 7).

Log ranks test showed that mGBA had a significantly later occurrence of cognitive impairment and hallucinations (compared to sGBA and rGBA) (Figure 2), and delusions (compared to sGBA and cGBA). There were no differences among groups as regard the onset of anxiety (p=0.4), ICB (p=0.3), dysautonomia (p=0.3), motor fluctuations (p=0.2), non-motor 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 PD patients. We detected *GBA* variants in 125 (14.3%) subjects, well above the 7-10% frequency reported in non-AJ populations.1,6,22-28

Previous screenings in two other Italian PD cohorts disclosed a frequency of 3-5%.8-10 However, these studies focused either on detecting the two commonest mutations (N370S and L444P) or on sequencing exons 9-10 only. Conversely, we detected 36 distinct variants, of which three novel. N370S and L444P were found in 47% patients, while mutations in exons 9-10 overall accounted for 58% positive cases only. These findings underlie two important concepts: 1) the frequency of *GBA*-related PD in Italy is among the highest worldwide among non-AJ populations; 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 commonest EOPD genes, such as *PARK2* and *PINK1*, or even *LRRK2*.

We observed significant differences of normalized GCase values in GBA-PD vs both healthy controls and NM-PD, as reported.30 When comparing enzymatic activity among different mutation classes, complex variants had the lowest activity while risk variants 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 GBA patients. Indeed, worse autonomic and cognitive functions in *de novo* PD predict development of ICB over the disease course,32 suggesting a close link of these symptoms as predictors of disease deterioration.

While 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 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 non-motor symptoms in carriers of severe variants.10,18-21 In the present study, we further addressed this issue by dividing GBA-PD patients into subgroups based on the variant type, and attempted to profile the clinical features which 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 shorter time to develop balance disturbances, higher risk of hallucinations and cognitive impairment. Subjects carrying complex variants had a similar phenotype, with comparable risk of hallucinations and dementia, but also 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 ones showing tremor-dominant phenotype at onset and later occurrence of non-motor fluctuations. When considering ICB in the four 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 Kaplan-Meier method for disease-duration scale time and log-rank tests for comparison of survival curves. Moreover, we acknowledge the lack of objective outcome measures to assess symptoms 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 also 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, in order to allow meaningful epidemiological comparisons.

In conclusion, GBA-PD has a high prevalence in the Italian population, also contributing to a significant proportion of EOPD cases. Our data expand the spectrum of non-motor 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 clinical trial focusing on GBA-PD.

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# Authors’ role

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

2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique

3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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# Appendix

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# Figure Legends

## Figure 1. Comparison of frequency of motor and non-motor symptoms among different groups.

(A) Frequency (%) of motor and non-motor symptoms in mutated (GBA-PD) vs non-mutated Parkinson Disease (NM-PD). \*significantly different comparisons (for details, see Supplementary Table 3). (B) Frequency (%) of motor and non-motor symptoms among GBA-PD subgroups carrying mild, complex, severe and risk variants. Statistical comparisons are reported in Supplementary Table 5. AKR: akinetic-rigid phenotype; H&Y, Hoehn and Yahr scale; ICB, impulsive compulsive behavior; MCI, mild cognitive impairment.

## Figure 2. Comparison of survival curves in GBA-mutated and non-mutated patients and in carriers of distinct types of *GBA* variants.

Kaplan-Meier method for disease-duration scale time and log-rank tests used for comparison of survival curves in mutated (GBA-PD) and non-mutated Parkinson Disease patients (NM-PD) (A-F), and in GBA carriers of mild, complex, severe and risk variants. (G-H). Log rank tests showed that GBA-PD patients developed anxiety, impulsive compulsive behavior (ICB), dysautonomia, non-motor fluctuations, hallucinations, delusions (not shown in figure, p<0.001) and cognitive impairment significantly earlier than NM-PD. Log rank tests also showed that severe and risk GBA manifested hallucinations and cognitive impairment earlier than mild GBA. Complex GBA had earlier hallucinations and cognitive impairment than mild GBA, albeit not significantly.

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