BRIEF REPORT

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

Simona Petrucci, MD, PhD,[1,2] Monia Ginevrino, PhD,[3,4] Ilaria Trezzi, MD,[5,6] Edoardo Monfrini, MD,[5,6] Lucia Ricciardi, MD, PhD,[7] Alberto Albanese, MD,[8] Micol Avenali, MD,[9,10] Paolo Barone, MD,[11] Anna Rita Bentivoglio, MD, PhD,[3,12] Vincenzo Bonifati, MD, PhD,[13] Francesco Bove, MD,[3,12] Laura Bonanni, MD, PhD,[14] Livia Brusa, MD,[15] Cristina Cereda, PhD,[9] Giovanni Cossu, MD,[16] Chiara Criscuolo, MD,[17] Giovanna Dati, BSc,[11] Anna De Rosa, MD, PhD,[17] Roberto Eleopra, MD,[18] Giovanni Fabbrini, MD,[1,19,20] Laura Fadda, MD, PhD,[21] Manuela Garbellini, BSc,[5,6] Brigida Minafra, MD,[9] Marco Onofrj, MD,[14] Claudio Pacchetti, MD,[9] Ilaria Palmieri, BSc,[9,22] Maria Teresa Pellecchia, MD, PhD,[11] Martina Petracca, MD,[3,12] Marina Picillo, MD, PhD,[11] Antonio Pisani, MD, PhD,[23] Annamaria Vallelunga, PhD,[11] Roberta Zangaglia, MD,[9] Alessio Di Fonzo, MD, PhD,[5,6] Francesca Morgante, MD, PhD,[7,24] and Enza Maria Valente, MD PhD[9,22*]

[1]*Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy* [2]*Department of Clinical and Molecular Medicine, S. Andrea University Hospital, Rome, Italy* [3]*Agostino Gemelli IRCCS University Hospital Foundation, Rome, Italy* [4]*Institute of Genomic Medicine, Catholic University, Rome, Italy* [5]*Foundation IRCCS Ca'Granda Ospedale Maggiore Policlinico, Neurology Unit, Milan, Italy* [6]*Dino Ferrari Center, Neuroscience Section, Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy* [7]*Neurosciences Research Centre, Molecular and Clinical Sciences Institute, St George's University of London, London, United Kingdom* [8]*Department of Neurology, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy* [9]*IRCCS Mondino Foundation, Pavia, Italy* [10]*Department of Brain and Behavioural Sciences, University of Pavia, Pavia, Italy* [11]*Center for Neurodegenerative Diseases, Department of Medicine, Surgery and Dentistry "ScuolaMedicaSalernitana," University of Salerno, Baronissi, SA, Italy* [12]*Institute of Neurology, Università Cattolica del Sacro Cuore, Rome, Italy* [13]*Department of Clinical Genetics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands* [14]*Department of Neuroscience, Imaging and Clinical Sciences, University G.d'Annunzio of Chieti-Pescara, Chieti, Italy* [15]*Parkinson Center, Neurology Complex Operative Unit, Sant'Eugenio Hospital, Rome, Italy* [16]*Brotzu Hospital, Neurology, Cagliari, Italy* [17]*Department of Neuroscience, Reproductive, and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy* [18]*Parkinson and Movement Disorders Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy* [19]*Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy* [20]*IRCCS Neuromed, Pozzilli (Isernia), Italy* [21]*Department of Neurology, University Hospital of Cagliari, Cagliari, Italy* [22]*Department of Molecular Medicine, University of Pavia, Pavia, Italy* [23]*Department of Systems Medicine, University of Roma Tor Vergata, Rome, Italy* [24]*Department of Experimental and Clinical Medicine, University of Messina, Messina, Italy*

*Correspondence to: Dr. Enza Maria Valente, Department of Molecular Medicine, University of Pavia, via Forlanini 14, 27100 Pavia, Italy; E-mail: enzamaria.valente@unipv.it

[Correction added on August 12, 2020 after first online publication: Alberto Albanese, affiliation updated.]

Simona Petrucci, Monia Ginevrino, and Ilaria Trezzi contributed equally. Alessio Di Fonzo, Francesca Morgante and Enza Maria Valente share senior authorship.

Funding agencies: Italian Ministry of Healthy (5 per mille to IRCCS Fondazione Mondino and Ricerca Corrente 2020 to E.M.V., PARKNET project to E.M.V. and A.D.F.); Stichting Parkinson Fonds, The Netherlands (to V.B.).
Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 2 April 2020; **Revised:** 17 May 2020; **Accepted:** 3 June 2020

Published online 00 Month 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28195

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 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.

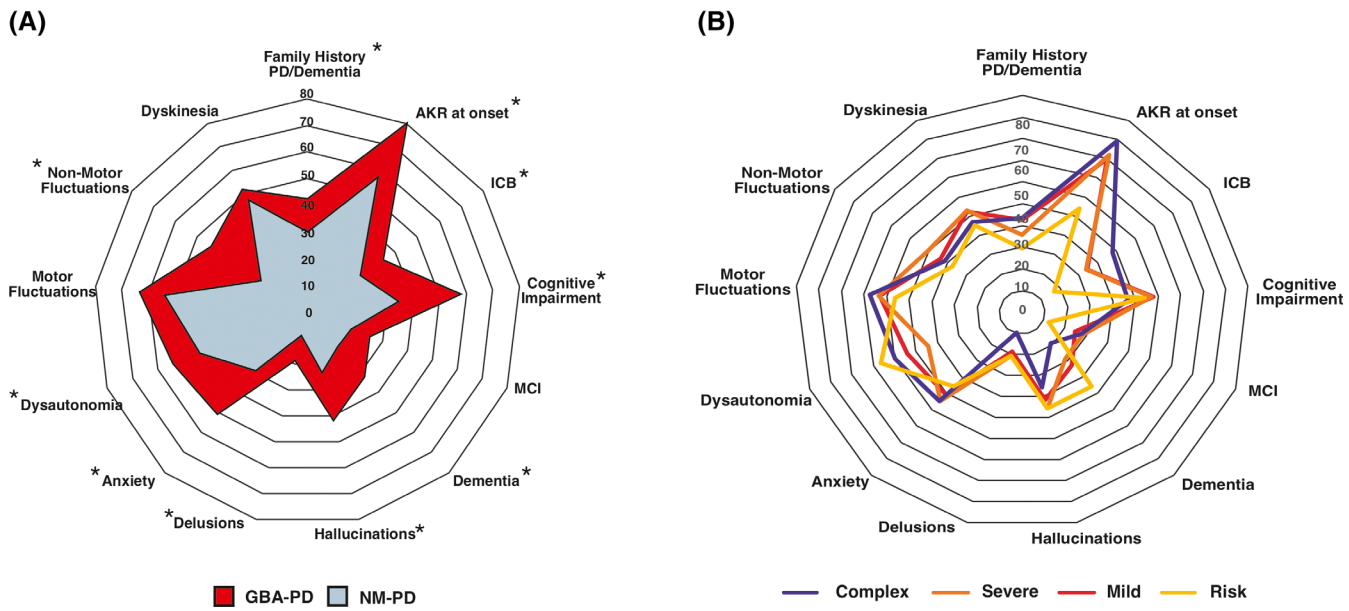

FIG. 1. Comparison of frequency of motor and nonmotor symptoms among different groups. (**A**) Frequency (%) of motor and nonmotor symptoms in GBA-PD versus NM-PD. (**B**) Frequency (%) of motor and nonmotor symptoms among GBA-PD subgroups carrying mild, complex, severe, and risk variants. Statistical 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.

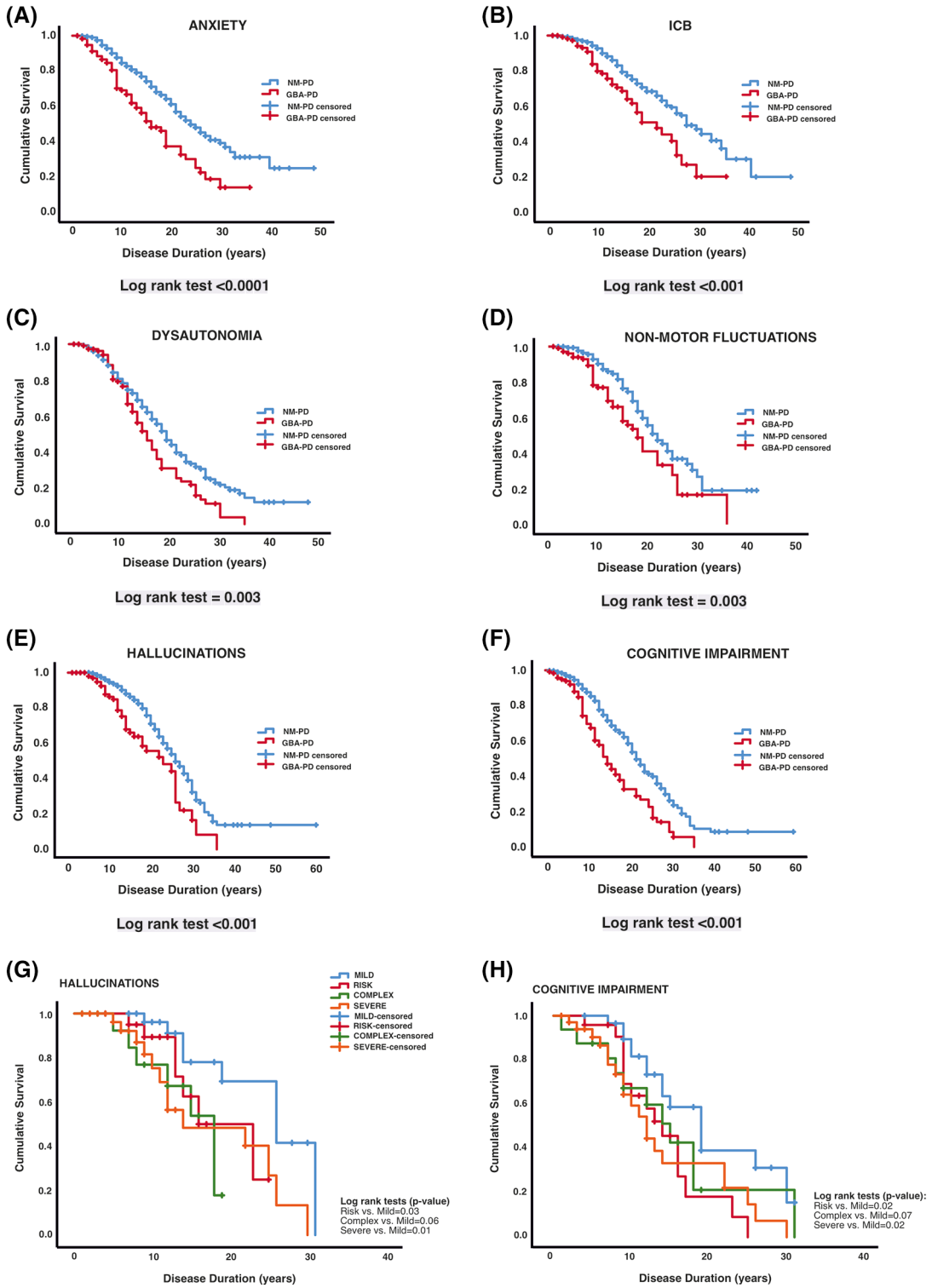

FIG. 2. Comparison of survival curves in GBA-PD versus NM-PD, and in carriers of distinct types of *GBA* variants. Kaplan-Meier method for disease-duration scale time and log-rank tests were used for comparison of survival curves in GBA-PD versus NM-PD (**A–F**) and in GBA carriers of mild, complex, 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.

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 nonmotor 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 nonmotor 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 nonmotor 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 ■

Acknowledgments: We are grateful to the patients and families for taking part in this study.

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).

References

1. Sidransky E, Nalls MA, Aasly JO, et al. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. New Engl J Med 2009;361:1651–1661.
2. Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a *GBA* mutation-positive cohort. JAMA Neurology 2015; 72:201–208.

3. Brockmann K, Srulijes K, Pflederer S, et al. GBA-associated Parkinson's disease: reduced survival and more rapid progression in a prospective longitudinal study. Mov Disord 2015;30:407–411.
4. Winder-Rhodes SE, Evans JR, Ban M, et al. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain 2013;136:392–399.
5. Gan-Or Z, Amshalom I, Kilarski LL, et al. Differential effects of severe vs mild GBA mutations on Parkinson disease. Neurology 2015;84:880–887.
6. Neumann J, Bras J, Deas E, et al. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain 2009; 132:1783–1794.
7. Zhang Y, Shu L, Zhou X, et al. A meta-analysis of GBA-related clinical symptoms in Parkinson's disease. Parkinsons Dis 2018;2018: 3136415.
8. De Marco EV, Annesi G, Tarantino P, et al. Glucocerebrosidase gene mutations are associated with Parkinson's disease in southern Italy. Mov Disord 2008;23:460–463.
9. Asselta R, Rimoldi V, Siri C, et al. Glucocerebrosidase mutations in primary parkinsonism. Parkinsonism Relat Disord 2014;20:1215–1220.
10. Cilia R, Tunesi S, Marotta G, et al. Survival and dementia in *GBA*-associated Parkinson's disease: the mutation matters. Ann Neurol 2016;80:662–673.
11. Quadri M, Yang X, Cossu G, et al. An exome study of Parkinson's disease in Sardinia, a Mediterranean genetic isolate. Neurogenetics 2015;16:55–64.
12. Beutler E, Demina A, Gelbart T. Glucocerebrosidase mutations in Gaucher disease. Mol Med 1994;1:82–92.
13. Torralba MA, Olivera S, Bureo JC, et al. Residual enzymatic activity as a prognostic factor in patients with Gaucher disease type 1: correlation with Zimran and GAUSS-I index and the severity of bone disease. QJM 2016;109:449–452.
14. Mallett V, Ross JP, Alcalay RN, et al. GBA p.T369M substitution in Parkinson disease: polymorphism or association? A meta-analysis. Neurol Genet 2016;2:e104.
15. Davis MY, Johnson CO, Leverenz JB, et al. Association of *GBA* mutations and the E326K polymorphism with motor and cognitive progression in Parkinson disease. JAMA Neurology 2016;73:1217–1224.
16. Duran R, Mencacci NE, Angeli AV, et al. The glucocerobrosidase E326K variant predisposes to Parkinson's disease, but does not cause Gaucher's disease. Mov Disord 2013;28:232–236.
17. Horowitz M, Pasmanik-Chor M, Ron I, Kolodny EH. The enigma of the E326K mutation in acid beta-glucocerebrosidase. Mol Genet Metab 2011;104:35–38.
18. Thaler A, Bregman N, Gurevich T, et al. Parkinson's disease phenotype is influenced by the severity of the mutations in the GBA gene. Parkinsonism Relat Disord 2018;55:45–49.
19. Lerche S, Wurster I, Roeben B, et al. Parkinson's disease: glucocerebrosidase 1 mutation severity is associated with CSF alpha-synuclein profiles. Mov Disord 2020;35:495–499.
20. Gan-Or Z, Giladi N, Rozovski U, et al. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology 2008;70:2277–2283.
21. Gan-Or Z, Giladi N, Orr-Urtreger A. Differential phenotype in Parkinson's disease patients with severe versus mild GBA mutations. Brain 2009;132:e125.
22. Lesage S, Anheim M, Condroyer C, et al. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet 2011;20:202–210.
23. Bras J, Paisan-Ruiz C, Guerreiro R, et al. Complete screening for glucocerebrosidase mutations in Parkinson disease patients from Portugal. Neurobiol Aging 2009;30:1515–1517.
24. Moraitou M, Hadjigeorgiou G, Monopolis I, et al. beta-Glucocerebrosidase gene mutations in two cohorts of Greek patients with sporadic Parkinson's disease. Mol Genet Metab 2011;104: 149–152.
25. Seto-Salvia N, Pagonabarraga J, Houlden H, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord 2012;27:393–399.
26. Pulkes T, Choubtum L, Chitphuk S, et al. Glucocerebrosidase mutations in Thai patients with Parkinson's disease. Parkinsonism Relat Disord 2014;20:986–991.
27. Barkhuizen M, Anderson DG, van der Westhuizen FH, Grobler AF. A molecular analysis of the GBA gene in Caucasian South Africans with Parkinson's disease. Mol Genet Genomic Med 2017;5: 147–156.
28. Liu G, Boot B, Locascio JJ, et al. Specifically neuropathic Gaucher's mutations accelerate cognitive decline in Parkinson's. Ann Neurol 2016;80:674–685.
29. Clark LN, Ross BM, Wang Y, et al. Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. Neurology 2007;69:1270–1277.
30. Alcalay RN, Levy OA, Waters CC, et al. Glucocerebrosidase activity in Parkinson's disease with and without GBA mutations. Brain 2015;138:2648–2658.
31. Morgante F, Fasano A, Ginevrino M, et al. Impulsive-compulsive behaviors in parkin-associated Parkinson disease. Neurology 2016; 87:1436–1441.
32. Ricciardi L, Lambert C, De Micco R, Morgante F, Edwards M. Can we predict development of impulsive-compulsive behaviours in Parkinson's disease? J Neurol Neurosurg Psychiatry 2018;89: 476–481.
33. Espay AJ, Kalia LV, Gan-Or Z, et al. Disease modification and biomarker development in Parkinson disease: revision or reconstruction? Neurology 2020;94:481–494.

Supporting Data

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Author Roles

(1) Research Project: A. Conception, Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.P.: 1B, 1C, 3A
M. Ginevrino: 1B, 1C, 3A
E.M.: 1B, 1C, 3A
I.T.: 1B, 1C, 3A
L.R.: 2A, 2B, 3A
A.A.: 1B, 3B
M.A.: 1C, 3A
P.B.: 1B, 3B
A.R.B.: 1B, 3B
V.B.: 1B, 1C, 3B
F.B.: 1B, 3B
L. Brusa: 1B, 3B
L. Bonanni: 1B, 3B
C. Cereda: 1B, 1C, 3B
G.C.: 1B, 3B
C. Criscuolo: 1B, 3B
G.D.: 1B, 1C, 3B
A.D.R.: 1B, 3B
R.E.: 1B, 3B
G.F.: 1B, 3B
L.F.: 1B, 3B
M. Garbellini: 1B, 1C, 3B
B.M.: 1B, 3B
M.O.: 1B, 3B
C.P.: 1B,3B
I.P.: 1B, 1C, 3B
M.T.P.: 1B, 3B
M. Petracca: 1B, 3B
M. Picillo: 1B, 3B
A.P.: 1B, 3B
A.V.: 1B, 1C, 3B
R.Z.: 1B, 3B
A.D.F.: 1A, 1B, 2C, 3B
F.M.: 1A, 2A, 2B, 3B
E.M.V.: 1A, 1B, 2C, 3B

Full financial disclosures for the previous 12 months: S. Petrucci, M. Ginevrino, I. Trezzi, E. Monfrini, M. Avenali, L. Brusa, C. Criscuolo, G. Dati, R. Eleopra, L. Fadda, M. Garbellini, B. Minafra, I. Palmieri, M. Petracca, A.M. Vallelunga, and R. Zangaglia report no disclosures. L. Ricciardi reports research support from UK's Medical Research Council and Clinical Academic Research Partnerships. A. Albanese reports research support from the European Community (Horizon 2020), Italian Ministry of Health, Fondazione Cariplo; Section Editor for *Frontiers in Neurology*; Associate Editor for *European Journal of Neurology*; and speaker honoraria from Ipsen and Merz. P. Barone reports advisory board fees from Zambon, Lundbeck, UCB, Chiesi, Abbvie, and Acorda. A.R. Bentivoglio reports speaker honoraria from Allergan, Ipsen, Merz, UCB Pharma, Bial, AbbVie, Zambon, and Boston. V. Bonifati reports research grants from the Stichting Parkinson Fonds (The Netherlands); the ZonMw (The Netherlands), under the aegis of the EU Joint Program Neurodegenerative Disease Research, the Centre for Human Drug Research (Leiden, The Netherlands); and the Erasmus MC, Rotterdam; compensation for serving as Section Editor of *Current*

Neurology and Neuroscience Reports and Editor-in-Chief of *Parkinsonism & Related Disorders*; honoraria from the International Parkinson and Movement Disorder Society; and coinventor in a patent titled: "Role for Low Density Lipoprotein Receptor-Related Protein in Progressive Brain Diseases." L. Bonanni reports research support from the Italian Ministry of Health and Mentis Cura, Oslo srl and teaching fees from G.E. Healthcare. F. Bove reports speaker honoraria from Abbvie. C. Cereda reports research support from Cariplo Foundation, Italian Ministry of Health, AIFA Foundation, and the Ministry of University and Research. G. Cossu reports speaker honoraria from UCB Pharma, Bial, AbbVie, Zambon, and Boston and research support from "Fondazione di Sardegna." A. De Rosa reports speaker honoraria from Lusofarmaco and UCB Pharma. G. Fabbrini reports speaker honoraria from Zambon and Abbvie and is a member of the editorial board of *Parkinsonism & Related Disorders*. M. Onofrj reports advisory board fees from GlaxoSmithKline, Novartis, Lundbeck, Eisai, Valeant, Medtronic, and Newron; speaker honoraria from Boehringer Ingelheim, GlaxoSmithKline, UCB, Zambon, the World Parkinson Congress, the Movement Disorder Society, and the Atypical Dementias congress; publishing royalties from Springer; member of the editorial boards of *Medicine (Baltimore)* and *Frontiers in Neuroscience*; and research support from the Italian Ministry of Health and the Italian Ministry of Education. C. Pacchetti reports speaking honoraria from AbbVie, Boston Scientific, Medtronic, and Zambon and research support from AbbVie, Boston Scientific, and Medtronic. M.T. Pellecchia reports advisory board fees from Lundbeck and Univar and research support from multiple system atrophy (MSA) Coalition and Agenzia Italiana del FArmaco. M. Picillo reports support from the Michael J. Fox Foundation for Parkinson's Research. A. Pisani reports speaking honoraria from Abbvie and Associate Editor of *Neurobiology of Disease* and *Frontiers in Neurology*. A. Di Fonzo reports advisory board fees from Sanofi and speaking honoraria from Sanofi and Zambon. F. Morgante reports speaking honoraria from Abbvie, Medtronic, Zambon, Bial, and Merz; travel grants from the International Parkinson and Movement Disorder Society; advisory board fees from Merz; consultancies fees from Merz and Bial; research support from Boston Scientific, Merz, and Global Kynetic; royalties for the book *Disorders of Movement* from Springer; and member of the editorial boards of *Movement Disorders*, *Movement Disorders Clinical Practice*, *European Journal of Neurology*. E.M. Valente reports speaking honoraria from Zambon; expert panelist for the International Parkinson and Movement Disorder Society; travel grants from the European Society of Human Genetics; Associate Editor of *Journal of Medical Genetics*; Section Editor of *Pediatric Research*; member of the editorial board of *Movement Disorders Clinical Practice*; research support from the Italian Ministry of Health, the CARIPLO Foundation, and the Pierfranco and Luisa Mariani Foundation.