Original Articles

Clinical prediction of *GBA* carrier status in Parkinson's disease

Julia Greenberg [a], Kelly Astudillo [a,b], Steven J. Frucht [a,b], Adeen Flinker [a,c,1], Giulietta M. Riboldi [a,b,*,1]

[a] *Department of Neurology, New York University Langone Health, New York, NY, USA*
[b] *The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, New York University Langone Health, New York, NY, USA*
[c] *Department of Biomedical Engineering, New York University Tandon School of Engineering, New York, NY, USA*

ABSTRACT

Introduction: Given the unique natural history of *GBA*-related Parkinson's disease (*GBA*-PD) and the potential for novel treatments in this population, genetic testing prioritization for the identification of *GBA*-PD patients is crucial for prognostication, individualizing treatment, and stratification for clinical trials. Assessing the predictive value of certain clinical traits for the *GBA*-variant carrier status will help target genetic testing in clinical settings where cost and access limit its availability.
Methods: In-depth clinical characterization through standardized rating scales for motor and non-motor symptoms and self-reported binomial information of a cohort of subjects with PD (n = 100) from our center and from the larger cohort of the Parkinson's Progression Marker Initiative (PPMI) was utilized to evaluate the predictive values of clinical traits for *GBA* variant carrier status. The model was cross-validated across the two cohorts.
Results: Leveraging non-motor symptoms of PD, we established successful discrimination of *GBA* variants in the PPMI cohort and study cohort (AUC 0.897 and 0.738, respectively). The PPMI cohort model successfully generalized to the study cohort data using both MDS-UPDRS scores and binomial data (AUC 0.740 and 0.734, respectively) while the study cohort model did not.
Conclusions: We assessed the predictive value of non-motor symptoms of PD for identifying *GBA* carrier status in the general PD population. These data can be used to determine a simple, clinically oriented model using either the MDS-UPDRS or subjective symptom reporting from patients. Our results can inform patient counseling about the expected carrier risk and test prioritization for the expected identification of *GBA* variants.

1. Introduction

Pathogenic variants in the glucocerebrosidase *(GBA)* gene currently represent one of the strongest risk factors for the development of Parkinson's Disease (PD) [1–4]. Biallelic variants of *GBA* are responsible for Gaucher's Disease (GD), a systemic lysosomal storage disease that presents with varying degrees of peripheral and central nervous system (CNS) involvement. GD presents with varying degrees systemic (GD type 1) and central nervous system (CNS) involvement (GD types 2 and 3) [5,6]. To date, more than 60 risk variants in the *GBA* gene have been described in association with PD [1,7,8]. Several cohort studies have delineated a distinct PD phenotype associated with *GBA* variants (*GBA*-PD) which, when compared to sporadic PD, is characterized by an earlier age of symptom onset, predominantly rigid-akinetic motor subtype, and more severe progression of non-motor symptoms including cognitive

impairment, hallucinations, dysautonomia, anxiety, and REM sleep behavior disorder (RBD) [2,9–11]. Given the unique natural history of *GBA*-PD and the potential for novel treatments in this population, identifying patients early is crucial for prognostication, individualizing treatment, and stratification for clinical trials [1,2]. However, the number of PD cases associated with *GBA* pathogenic variants remains relatively small and resources for genetic testing may be limited in certain setting. Prioritizing patients for genetic testing remains a challenge, because while a *GBA*-PD phenotype is easily discernible at the population level, overlaps between *GBA*-PD and idiopathic PD phenotypes exist on the individual level [12]. Assessing pre-test probability would prove useful to help target genetic testing in clinical settings and to counsel patient about likelihood of a positive genetic status.

In this work, we performed an in-depth clinical and genetic characterization of a cohort of patients with PD, and used this data to design a

clinically oriented statistical model for identifying clinical traits predictive of *GBA*-variant carrier status and quantify their predictive value. We used a combination of clinical features to generate a model for predicting the presence of *GBA* variants, using a cohort of subjects from the Parkinson's Progression Marker Initiative (PPMI), and validated the results in a cohort of PD patients from our center. In order to make the model as broadly applicable as possible, we compared the validity of dichotomous, self-reported ratings with standardized rating scales for characterization of non-motor symptoms in PD and applied the model to both.

2. Methods

2.1. PPMI cohort

The Parkinson's Progressive Marker Initiative (PPMI) is a multi-center, international observational study of people with PD and non-affected controls. The study gathers clinical and biological data in a large, publicly accessible bio registry with the aim of identifying significant biomarkers of PD onset and progression. We utilized the latest available dataset, which was downloaded from the University of Southern California Laboratory of Neuroimaging (LONI) in January 2021. The selected cohort consisted of subjects at the time of enrollment (baseline visit or BL) and at a follow-up visit 5 years after enrollment (visit 12 or V12). All subjects were enrolled within 2 years of initial PD diagnosis, and were not on any PD-related medications at the time of enrollment. Detailed information about the PPMI study and included data can be found at https://www.ppmi-info.org. For our study we selected only subjects with a diagnosis of Parkinson's disease.

2.2. Study cohort

We enrolled a cohort of subjects between ages 18 and 80 years with a diagnosis of Parkinson's disease confirmed clinically by a board-certified neurologist according to standard diagnostic criteria [13]. The current study was approved by the Institutional Review Board (IRB) at the New York University School of Medicine. Subjects were enrolled upon signing an informed consent approved by the IRB of New York University School of Medicine. For each subject, basic demographic data (gender, age, age of onset, ethnicity and race), a focused medical history, and a complete Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) were collected.

Additional data was collected for a variety of non-motor symptoms, including cognitive impairment, anxiety, depression, autonomic symptoms, and REM sleep behavior disorder (RBD) via patient-reported binary responses and symptom-specific validated rating scales. Patient self-reported responses were collected via a series of binary 'yes/no' questions for each of the non-motor symptoms listed above (i.e. "Do you have anxiety? Depression?"). For MDS-UPDRS part I subscores each symptom was defined as subscore >0. For assessment of REM sleep behavior disorder, which is highly associated with PD but not assessed on the standard MDS-UPDRS, the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) was used, with RBD defined as score ≥5 [14,15].

2.3. Genetic analysis

For the study cohort blood samples were collected for each subject. Samples were sent for sequencing of the *GBA* gene at a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory. In brief, Next Generation Sequencing (NovaSeq 9000 platform, paired-end 100 bp reads) was utilized to analyze the exonic regions, intron/exon splice junctions, intronic, promoter regions, and UTR, containing previously reported pathogenic variants. A locus-specific 6.5 kb amplicon for *GBA* was generated with long-range PCR and then prepared for short-read NGS. Sanger sequencing with specific amplicons was utilized to validate the variants detected by NGS and for the analysis of regions with a low coverage (<20×).

2.4. Identification of predictive traits for GBA status

A statistical model for predicting *GBA*-variant status was developed using the PD-associated non-motor symptoms collected from the study cohort [2,9,10,12,16,17]. Motor symptoms were not included because the MDS-UPDRS part III is not reflective of a specific motor feature – a high score can be due to any number of motor symptoms ranging from rigidity to tremor to postural instability and would therefore be challenging to interpret. In addition, on/off states were not consistent across all subjects in the study cohort at the time of the clinic visit when the MDS-UPDRS was performed. The features included in the final model were: age of symptom onset, ancestry (Ashkenazi Jewish or 'other'), cognitive impairment, anxiety, hallucinations, orthostatic hypotension, constipation, urinary symptoms, and RBD. All non-motor symptoms except for RBD were defined by the appropriate MDS-UPDRS scale subscore, with the threshold for symptom positivity of >0 [13]. Because RBD is not included in the MDS-UPDRS, statistical analyses for RBD were performed using symptom severity as determined by the REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), with the threshold for symptom positivity defined as a total score ≥5 [14,15].

For each feature, any missing values were replaced with the median value (i.e. Missing Value Imputation) and a logistic regression model was fit to predict *GBA*-variant status. Feature importance statistical values were reported based on the coefficient's p-value of the general linear model (using a logit link function). The degree of importance was quantified as the difference between the AUC (area under the curve) of the baseline model (all features included) and the AUC of the model trained without the feature (Fig. 1C, D).

Multiple models were generated, one for the study cohort and two for the PPMI cohort (one using the BL cohort data and one using V12 cohort data; though only the V12 model was used for subsequent analyses owing to its better performance). The study cohort and PPMI V12 models were each applied on their respective cohorts (Fig. 1A, B) and were then cross-validated against the other cohort (Fig. 2A, B), with non-motor symptoms defined according to MDS-UPDRS subscores as described above.

The PPMI V12 model was also applied on the study cohort data with non-motor symptoms defined according to subjects' self-reported binary (yes/no) responses (Fig. 2C) in order to assess comparability of the model performance on self-reported versus MDS-UPDRS determined non-motor symptoms.

In order to assess the comparability of different statistical approaches, analogous models for the PPMI data, study cohort data, and an additional combined data set (PPMI + study cohort) were compared across the general logistic regression function model used above, a random forest model, and a support vector machine model, using both a five-fold and leave-one-out cross validation approach (Supplemental Fig. 1). The random forest and support vector machine models were validated against each cohort, similar to the logistic regression models described above (Supplementary Figs. 2 and 3).

All statistical analyses were conducted using custom code written in Matlab R2022b.

Comparison of symptom assessments based on self-reported data and MDS-UPDRS sub-scores.

For the study cohort, a pairwise statistical comparison of the MDS-UPDRS subscores and their matched self-reported symptoms was conducted using Spearman correlations (See Table 1 for details). First, any missing values (no response in the rating scale or self-report) were removed from comparison, yielding a sample size range of 91–100 per statistical comparison (mode of 100 samples, median of 95 samples, exact sample sizes are reported in Table 1). All MDS-UPDRS subscores were converted to binary categorical variables by contrasting "Normal" vs. other ratings or "Never" vs. other ratings, and by employing a
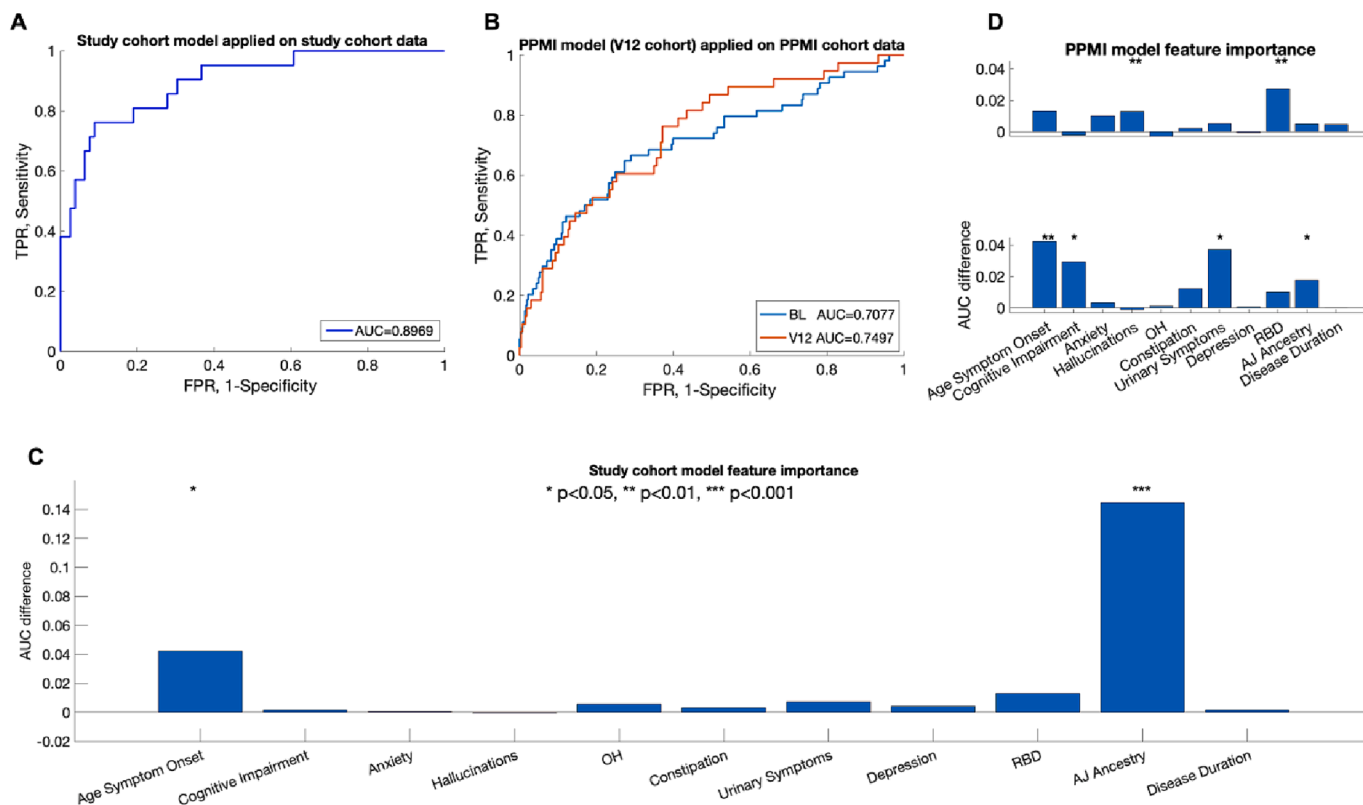
Fig. 1. Performance of the *GBA* predictive model generated using study cohort data and PPMI data. Receiver operating curves (ROCs) depict performance of (A) the study cohort model and (B) the PPMI model at visits longitudinally across time, with non-motor symptoms measured via MDS-UPDRS subscores. Relative feature importance for each trait is shown for (C) the study cohort model and (D) the PPMI model, calculated using a logit link function. (*) = degree of significance. BL = baseline visit, V12 = visit 12.
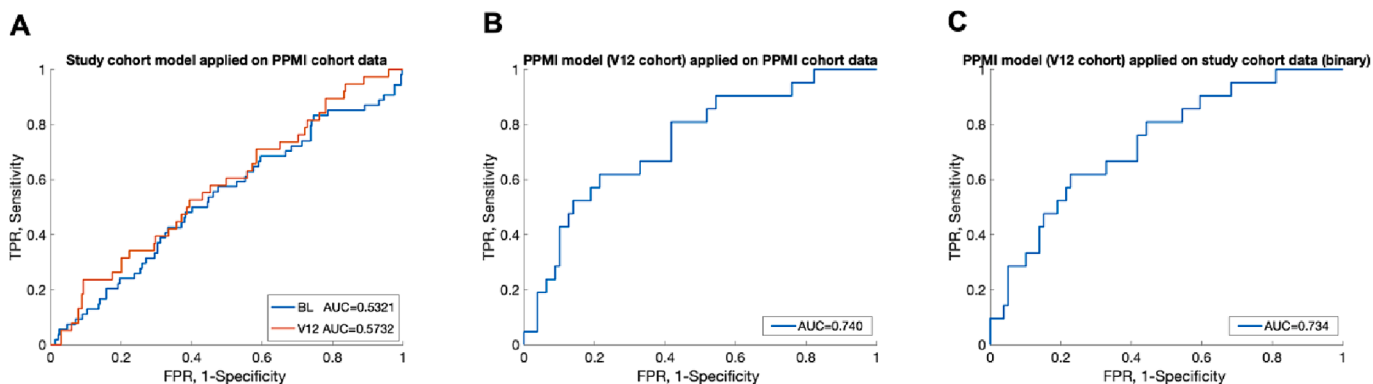

Fig. 2. Generalizability of the study cohort and PPMI cohort *GBA* predictive models. Receiver operating curves (ROCs) depict (A) the performance of the study cohort model on the PPMI cohort data, and (B, C) the performance of the PPMI cohort model on the study cohort data, with non-motor symptoms measured via MDS-UPDRS subscores and via subjects' self-reported binary answers. BL = baseline visit, V12 = visit 12.

threshold for the RBDSQ (RBDSQ ≥ 5). The resultant binary variables were the 'yes'/'no' self-reported symptom and the matching binary validating rating scale. A Spearman correlation was conducted on each pair reported in Table 1. In the Supplementary Tables, the frequency of traits were compared between *GBA*-PD and non-*GBA*-PD subjects and differences between the two groups were tested for significance using a chi square test for independence (binarized data, 'positive' or 'negative' for each symptom) and Wilcoxon rank sum test (discrete data, actual value for each scale).

3. Results

3.1. Clinical characterization of the cohorts

Detailed demographic data and comparison of non-motor symptoms for the study cohort and PPMI cohorts (BL and V12) can be found in Supplementary Tables 1-5. A total of 100 subjects were included in the study cohort, 21 of whom had single or multiple *GBA* variants identified. 76 % of the *GBA*-PD subjects were of AJ descent, compared to only 25 % of the non-*GBA*-PD subjects (Supplementary Table 1). 420 subjects were included in the BL PPMI cohort (54 *GBA*-PD and 366 non-*GBA*-PD) and 307 subjects were included in the V12 PPMI cohort (38 *GBA*-PD and 269

Table 1

Comparison of validated scales and self-reported binary responses for assessment of non-motor symptoms in PD (study cohort). Pairwise comparison of MDS-UPDRS subscales and binary features using Spearman's rank correlations. (*) = p < 0.05. Significant thresholds for each rating scale are reported in the manuscript. MDS-UPDRS = Movement Disorder Society-Unified Parkinson's Disease Rating Scale.

Symptom	MDS-UPDRS Subscale	Sample Size (n)	Met Scale Threshold for Symptom Positivity n (%)	Self-Reported Symptom n (%)	Comparison MDS-UPDRS vs Self-Reported Symptoms (Spearman's ρ, p-value)
Cognitive Impairment	MDS-UPDRS 1.1	100	22 (22 %)	21 (21 %)	−0.62, <0.001*
Depression	MDS-UPDRS 1.3	100	37 (37 %)	33 (33 %)	−0.78, <0.001*
Anxiety	MDS-UPDRS 1.4	100	53 (53 %)	46 (46 %)	−0.55, <0.001*
Hallucinations	MDS-UPDRS 1.2	100	7 (7 %)	9 (9 %)	−0.74, <0.001*
Orthostatic Hypotension	MDS-UPDRS 1.12	93	31 (33 %)	29 (29 %)	−0.76, <0.001*
Constipation	MDS-UPDRS 1.11	93	41 (44 %)	44 (44 %)	0.65, <0.001*
Urinary Symptoms	MDS-UPDRS 1.10	93	40 (43 %)	44 (44 %)	−0.65, <0.001*
REM sleep Behavior Disorder (RBD)	REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	91	33 (36 %)	39 (39 %)	0.61, <0.001*

non-*GBA*-PD) (Supplementary Table 3). 19 % of *GBA*-PD subjects in the BL cohort and 10.5 % of *GBA*-PD subjects in the V12 cohort were of AJ descent, compared to 6 % of non-*GBA*-PD subjects in the BL cohort and 4.5 % of non-*GBA*-PD subjects in the V12 cohort (Supplementary Table 3). Of note, ancestry data was not available for 47 % of subjects in the BL cohort, and for 80 % of subjects in the V12 cohort).

The average age of symptom onset was younger for *GBA*-PD subjects than for non-*GBA*-PD subjects in the study and both PPMI cohorts, consistent with previous data reported in the literature (Supplementary Tables 1 and 3) (24). The mean age at time of study enrollment was also consistently younger for *GBA*-PD subjects across the cohorts (Supplementary Tables 1 and 3).

The only statistically significant differences in non-motor symptoms between the *GBA*-PD and non-*GBA*-PD subjects were a higher frequency of urinary symptoms among non-*GBA*-PD subjects in the study cohort (Supplementary Table 2), and a higher frequency of hallucinations in the *GBA*-PD subjects in the PPMI BL cohort (Supplementary Table 4). Non-*GBA*-PD subjects in the study cohort displayed statistically significantly higher scores on the MDS-UPDRS part I (p = 0.04), but there were no significant differences between the groups on MDS-UPDRS parts II–IV. There were no statistically significant differences in MDS-UPDRS parts I–IV individually or MDS-UPDRS total scores between the *GBA* and non-*GBA*-PD subjects at any of the 6 visits (data not shown). Scores for MDS-UPDRS part IV were not calculated for the PPMI baseline cohort, as subjects were not on dopaminergic medications at the time of study enrollment.

3.2. GBA screening

We identified 4 established pathogenic variants of *GBA* in the study cohort (N409S in 13 subjects, R535H in 1 subject, L29Afs*18 in 1 subject, H294Q in 1 subject), 1 established PD risk variant (E365K in 4 subjects), and 2 variants of unknown significance or likely pathogenic (Q182 = in 1 subject, W387G in 1 subject) [2,5,16,18]. Literature regarding Q182 = and W387G variants remains limited [3,8,18]. In the selected PPMI cohort, genetic analysis identified 8 established pathogenic *GBA* variants (N409S in 8 subjects, L483P in 1 subject, A495P in 2 subjects, G154R in 1 subject, IVS2 + 1G > A in 1 subject, L29Afs*18 in 1 subject, R502C in 1 subject, R83C in 2 subjects, R159W in 1 subject), 3 established PD risk variants (E365K in 21 subjects, T408M in 11 subjects), and 2 possible risk variants (I528L in 1 subject, R78C in 2 subjects) [8,18].

3.3. Clinical and demographic traits predictive for GBA genotype and quantification of their predictive value

In order to identify which non-motor symptoms of PD and demographic features were most predictive of *GBA* variant status and quantify their predictive values, we built a predictive model leveraging

demographic information and MDS-UPDRS subscores. We first generated a model with the data from the PPMI cohort BL and V12 populations (BL and V12 PPMI cohort models) that was tested on the PPMI cohort data. The BL and V12 models had predictive values of 0.7077 and 0.7378, respectively (Fig. 1A, B). The traits that drove the PPMI model's performance were AJ ancestry, age of symptom onset, cognitive impairment, and urinary symptoms (Fig. 1D). When tested against the study cohort data, the PPMI V12 model yielded AUCs of 0.740 (non-motor symptoms measured via MDS-UPDRS subscores).

Our results showed that self-reported binary symptoms reflected outcomes on the MDS-UPDRS subscales for all non-motor symptoms, and on the RBDSQ (Table 1). Because of this the PPMI V12 model was also tested against the study cohort with non-motor symptoms measured via self-reported binary symptoms yielding a AUC of 0.734 (Fig. 2B, C).

When an analogous model was created using the study cohort data, the resultant AUC for the model was 0.8969 when applied on the study cohort data with non-motor symptoms measured via MDS-UPDRS subscores (Fig. 1A). AJ ancestry and younger age of onset were the only statistically significant features in the study cohort model (Fig. 1C). When tested against the PPMI cohort V12 data, the study cohort model yielded an AUC of 0.5738 (Fig. 2A).

In order to estimate the generalizability of our models we use both a Five-fold (5F) and leave one out (LOO) cross validation applied across three modeling approaches (GLM, RF, SVM). These models showed consistent results both in the study cohort and the combined cohort (Supplementary Fig. 1). For the PPMI cohort, the GLM showed greater AUC (5F = 0.642; LOO = 0.642) compared to RF (5F = 0.580; LOO = 0.540) and SVM (only for 5F = 0.536) (Supplementary Fig. 1).

AUCs for the PPMI and study cohort models using SVM modeling yielded AUCs of 0.5866 and 0.8752, respectively – slightly poorer performance than those obtained using linear regression models (Supplementary Fig. 2A, B). Similar AUCs were obtained for the study cohort model's performance on the PPMI cohort when random forest (AUC 0.5422) and support vector machine (0.5748) models were used (Supplementary Fig. 3A). RF and SVM modeling resulted in slightly poorer model performance for the PPMI model on the study cohort (random forest – AUC 0.589 for PPMI model on study cohort data, 0.569 for PPMI model on study cohort data (binary); small vector machine – AUC 00.769 for PPMI model on study cohort data, 0.727 for PPMI model on study cohort data (binary)) (Supplementary Fig. 3B,C).

4. Discussion

Prioritization of gene testing and appropriate pre-test probability counseling are important in the context of Parkinson's disease as genetic tests become more available and more relevant also for therapeutic implications. We developed a simple statistical model to identify clinical and demographic features associated with *GBA* variant status and ascertain their predictive value. Our model was developed using a

combination of clinical and demographic features from a cohort of PD subjects from the PPMI database (PPMI cohort model) and validated the model against a cohort at our center (AUC = 0.734, Fig. 2B). In our model, Ashkenazi Jewish (AJ) ancestry and younger age of symptom showed the highest predictive value, followed by the presence of cognitive impairment and urinary symptoms (Fig. 1D).

The model was initially built leveraging the sub-scores from the MDS-UPDRS scale. Although MDS-UPDRS is widely used, many retrospective studies or in-office evaluation of clinical traits are based on self-reported positive or negative response in regards to motor and non-motor symptoms associated with PD. Importantly, we showed that for all non-motor symptoms included in the model, self-reported binary (yes/no) responses accurately reflect outcomes on MDS-UPDRS sub-scales (Table 1) and that the PPMI model performed equally well on this self-reported data (Fig. 2C). This makes the model valuable also in the context of clinical setting assessments.

Different statistical approaches (RF and SVM) showed consistent results in the two cohorts (study cohort and PPMI cohort) and the combined cohorts, except for slightly poorer performance of the RF modelling on the PPMI cohort (Supplementary Fig. 1–2).

One limitation of the model as it currently stands is the exclusion of motor symptoms, which if included could increase the model's accuracy. A decision was made to exclude the MDS-UPDRS part III because (1) as described above, the cause of a high score is not uniform and may reflect a number of different motor features; and (2) the time of subjects' dopaminergic medications relative to MDS-UPDRS administration was not controlled for in the study cohort, leading to potentially inconsistent on/off states which would have skewed results. PD-related medications were also not controlled for. It is also important to note that the study cohort model did not generalize well to the larger PPMI cohort, which is likely in part due to intrinsic differences between the study cohort and PPMI populations (such as relatively younger age of onset in the study cohort), small sample size and sample bias in the study cohort including an overrepresentation of subjects with Ashkenazi Jewish ancestry (Fig. 2A). In addition, the entity of missing data entries for ancestry in the PPMI cohort likely negatively affected results given the important contribution of ancestry to the model's performance. Lastly, different *GBA* variants may affect PD phenotypic expression and disease progression differently, which was not accounted for when creating the current model due to small sample size for each given variant in the study cohort [9,19]. For instance, two subjects in the study cohort were compound heterozygotes for *GBA* and *LRRK2*, a genotype which has been correlated with milder non-motor symptoms compared to *GBA*-PD [19,20]. Although we acknowledge the differences between the two cohorts, the fact that the PPMI model generalizes well to the study cohort further reinforces the strength of the proposed model.

When we characterized our cohort, surprisingly, we identified only a few statistically differences in non-motor symptoms between *GBA*-PD and non-*GBA*-PD subjects in our study cohort and in the PPMI cohort (Supplementary Tables 2 and 5). Although in the study cohort the majority of non-motor symptoms showed a trend towards higher rates among non-*GBA*-PD subjects, the difference was only statistically significant for urinary symptoms, and the only statistically significant difference in the PPMI cohort was frequency of hallucinations (Supplementary Tables 2 and 5). This is contrary to a number of previous studies that found statistically significant differences in the rates of non-motor symptoms in *GBA*-PD and non-*GBA*-PD [21–25]. These studies, however, followed patients with longer disease duration, utilized different scales to measure non-motor symptoms, and/or analyzed data using different scales, all of which provide possible explanations for this discrepancy [12,16,21–25].

In summary, we describe a simple, clinically oriented model that helps to quantify the predictive value of specific demographic and non-motor features for *GBA* carrier status. We hope that these results will help to guide genetic testing in clinical settings where resources are limited, by selecting patients with clinical features that are most

associated with pathogenic variants of *GBA,* specifically AJ ancestry, young age of symptom onset, cognitive impairment, and urinary symptoms.

5. Study sponsorship or funding information

Prevail Therapeutics.

6. Statistical analysis and list affiliation(s)

Dr. Adeen Flinker, Department of Biomedical Engineering, New York University Tandon School of Engineering, New York, NY, United States of America.

7. Posting on a preprint server (e.g., bioRxiv)

Not applicable.

8. Disclosures

Dr. Riboldi is supported by grants from Michael J Fox Foundation, Parkinson's Foundation, Department of Defense (PD210038), NIH (R01NS 116006; R01NS133742), and received a previous research grant from Prevail Therapeutics. Dr. Flinker is supported by grants from the NIH (R01NS109367, R01DC018805, R01NS115929) and NSF (CRCNS 1912286). J.G., K.A., and S.F. report no specific funding related to this work. Dr. Frucht reports no disclosures. Dr. Greenberg reports no disclosures. Ms. Astudillo reports no disclosures.

9. Financial disclosures for the previous 12 months

The authors declare that there are no additional disclosures to report.

10. Ethical compliance statement

The current study was approved by the institutional review board at the New York University School of Medicine. Informed consent was obtained from all participants in the study. Permission was obtained to use the MDS-UPDRS and SCOPA-AUT rating scales. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

CRediT authorship contribution statement

Julia Greenberg: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kelly Astudillo:** Writing – review & editing, Investigation, Data curation. **Steven J. Frucht:** Writing – review & editing, Supervision. **Adeen Flinker:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis. **Giulietta M. Riboldi:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giulietta Maria Riboldi reports financial support was provided by Prevail Therapeutics. G.R. is supported by grants from Michael J Fox Foundation, Parkinson's Foundation, Department of Defense (PD210038), NIH (R01NS116006, R01NS133742), and received a previous research grant from Prevail Therapeutics. A.F. is supported by grants from the NIH (R01NS109367, R01DC018805, R01NS115929) and NSF (CRCNS 1912286). J.G., K.A., and S.F. report no specific funding related to this work. Financial Disclosures for the Previous 12 Months: The authors declare that there are no additional disclosures to

report.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prdoa.2024.100251.

References

[1] K.A. Senkevich, A.E. Kopytova, T.S. Usenko, A.K. Emelyanov, S.N. Pchelina, Parkinson's disease associated with GBA gene mutations: molecular aspects and potential treatment approaches, Acta Nat. 13 (2) (2021) 70–78, https://doi.org/10.32607/actanaturae.11031.

[2] E. Menozzi, A.H.V. Schapira, Exploring the genotype-phenotype correlation in GBA-Parkinson disease: clinical aspects, biomarkers, and potential modifiers, Front. Neurol. 12 (2021) 694764, https://doi.org/10.3389/fneur.2021.694764. Published 2021 Jun 24.

[3] Z. Gan-Or, I. Amshalom, L.L. Kilarski, et al., Differential effects of severe vs mild GBA mutations on Parkinson disease, Neurology 84 (9) (2015) 880–887, https://doi.org/10.1212/WNL.0000000000001315.

[4] W.C. Nichols, N. Pankratz, D.K. Marek, M.W. Pauciulo, V.E. Elsaesser, C.A. Halter, et al., Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset, Neurology 72 (4) (2009) 310–316, https://doi.org/10.1212/01.wnl.0000327823.81237.d1. Epub 20081105.

[5] A. Greuel, J.P. Trezzi, E. Glaab, et al., GBA variants in Parkinson's disease: clinical, metabolomic, and multimodal neuroimaging phenotypes, Mov. Disord. 35 (12) (2020) 2201–2210, https://doi.org/10.1002/mds.28225.

[6] E. Sidransky, G. Lopez, The link between the GBA gene and parkinsonism, Lancet Neurol. 11 (11) (2012) 986–998, https://doi.org/10.1016/S1474-4422(12)70190-4.

[7] C. Blauwendraat, J.M. Bras, M.A. Nalls, et al., Coding variation in GBA explains the majority of the SYT11-GBA Parkinson's disease GWAS locus, Mov. Disord. 33 (11) (2018) 1821–1823, https://doi.org/10.1002/mds.103.

[8] S.C. Parlar, F.P. Grenn, J.J. Kim, C. Baluwendraat, Z. Gan-Or, Classification of GBA1 variants in Parkinson's disease: The GBA1-PD browser, Mov. Disord. (2023), https://doi.org/10.1002/mds.29314. Epub 20230104.

[9] S. Petrucci, M. Ginevrino, I. Trezzi, E. Monfrini, L. Ricciardi, A. Albanese, et al., GBA-related Parkinson's disease: dissection of genotype-phenotype correlates in a large Italian cohort, Mov. Disord. 35 (11) (2020) 2106–2111, https://doi.org/10.1002/mds.28195.

[10] A. Thaler, T. Gurevich, A. Bar Shira, M. Gana Weisz, E. Ash, T. Shiner, et al., A "dose" effect of mutations in the GBA gene on Parkinson's disease phenotype, Parkinsonism Relat. Disord. 36 (2017) 47–51, https://doi.org/10.1016/j.parkreldis.2016.12.014. Epub 20161216.

[11] J. Maple-Grodem, I. Dalen, O.B. Tysnes, A.D. Macleod, L. Forsgren, C.E. Counsell, et al., Association of GBA genotype with motor and functional decline in patients with newly diagnosed Parkinson disease, Neurology 96 (7) (2021) e1036–e1044, https://doi.org/10.1212/WNL.0000000000011411. Epub 20201221.

[12] S.E. Winder-Rhodes, J.R. Evans, M. Ban, S.L. Mason, C.H. Williams-Gray, T. Foltynie, et al., Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort, Brain 136 (Pt 2) (2013) 392–399, https://doi.org/10.1093/brain/aws318.

[13] R.B. Postuma, W. Poewe, I. Litvan, S. Lewis, A.E. Lang, G. Halliday, et al., Validation of the MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 33 (10) (2018) 1601–1608, https://doi.org/10.1002/mds.27362. Epub 20180825.

[14] K. Stiasny-Kolster, G. Mayer, S. Schafer, J.C. Moller, M. Heinzel-Gutenbrunner, W.H. Oertel, The REM sleep behavior disorder screening questionnaire–a new diagnostic instrument, Mov. Disord. 22 (16) (2007) 2386–2393, https://doi.org/10.1002/mds.21740.

[15] T. Nomura, Y. Inoue, T. Kagimura, Y. Uemura, K. Nakashima, Utility of the REM sleep behavior disorder screening questionnaire (RBDSQ) in Parkinson's disease patients, Sleep Med. 12 (7) (2011) 711–713, https://doi.org/10.1016/j.sleep.2011.01.015. Epub 20110622.

[16] J. Aharon-Peretz, H. Rosenbaum, R. Gershoni-Baruch, Mutations in the glucocerebrosidase gene and Parkinson's disease in Ashkenazi Jews, N. Engl. J. Med. 351 (19) (2004) 1972–1977, https://doi.org/10.1056/NEJMoa033277.

[17] L. Krohn, J.A. Ruskey, U. Rudakou, E. Leveille, F. Asayesh, M.T.M. Hu, et al., GBA variants in REM sleep behavior disorder: A multicenter study, Neurology 95 (8) (2020) e1008–e1016, https://doi.org/10.1212/WNL.0000000000010042. Epub 20200626.

[18] J.M. den Heijer, V.C. Cullen, M. Quadri, A. Schmitz, D.C. Hilt, P. Lansbury, et al., A large-scale full GBA1 gene screening in Parkinson's disease in the Netherlands, Mov. Disord. 35 (9) (2020) 1667–1674, https://doi.org/10.1002/mds.28112. Epub 20200702.

[19] N. Omer, N. Giladi, T. Gurevich, A. Bar-Shira, M. Gana-Weisz, O. Goldstein, et al., A possible modifying effect of the G2019S mutation in the LRRK2 gene on GBA Parkinson's disease, Mov. Disord. 35 (7) (2020) 1249–1253, https://doi.org/10.1002/mds.28066. Epub 20200430.

[20] R.A. Ortega, C. Wang, D. Raymond, et al., Association of dual LRRK2 G2019S and GBA variations with Parkinson disease progression, JAMA Netw. Open 4 (4) (2021) e215845, https://doi.org/10.1001/jamanetworkopen.2021.5845. Published 2021 Apr 1.

[21] F. Blandini, R. Cilia, S. Cerri, G. Pezzoli, A.H.V. Schapira, S. Mullin, et al., Glucocerebrosidase mutations and synucleinopathies: Toward a model of precision medicine, Mov. Disord. 34 (1) (2019) 9–21, https://doi.org/10.1002/mds.27583. Epub 20181227. PubMed PMID: 30589955.

[22] M. Avenali, M. Toffoli, S. Mullin, A. McNeil, D.A. Hughes, A. Mehta, et al., Evolution of prodromal parkinsonian features in a cohort of GBA mutation-positive individuals: a 6-year longitudinal study, J. Neurol. Neurosurg. Psychiatry. 90 (10) (2019) 1091–1097, https://doi.org/10.1136/jnnp-2019-320394. Epub 20190620.

[23] S. Mullin, M. Beavan, J. Bestwick, A. McNeill, C. Proukakis, T. Cox, et al., Evolution and clustering of prodromal parkinsonian features in GBA1 carriers, Mov. Disord. 34 (9) (2019) 1365–1373, https://doi.org/10.1002/mds.27775. Epub 20190628.

[24] K. Brockmann, K. Srulijes, A.K. Hauser, C. Schulte, I. Csoti, T. Gasser, et al., GBA-associated PD presents with nonmotor characteristics, Neurology. 77 (3) (2011) 276–280, https://doi.org/10.1212/WNL.0b013e318225ab77. Epub 20110706.

[25] S. Jesus, I. Huertas, I. Bernal-Bernal, M. Bonilla-Toribio, M.T. Caceres-Redondo, L. Vargas- Gonzalez, et al., GBA variants influence motor and non-motor features of Parkinson's disease, PLoS One 11 (12) (2016) e0167749, https://doi.org/10.1371/journal.pone.01677. Epub 20161228.