A disease progression model to quantify the non-motor symptoms of Parkinson’s disease in participants with leucine-rich repeat kinase 2 mutation

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CONFLICT OF INTEREST

MaA was a full-time employee of Merck and is currently a full-time employee of Amgen.

MB, BB, and HS are employees of UCB.

GP is a full-time employee of F. Hoffmann-La Roche Ltd.

VS, NM, KLY, FG, JA are employees of Merck.

MY is an employee of Biogen.
CC is an employee of GlaxoSmithKline.

JW is an employee of Lundbeck.

SM and VT are employees of Sanofi.

YH is an employee of Takeda.

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Abstract

Leucine-rich repeat kinase 2 (LRRK2) inhibitors are currently in clinical development as interventions to slow progression of Parkinson’s disease (PD). Understanding the rate of progression in PD as measured by both motor and non-motor features is particularly important in assessing the potential therapeutic effect of LRRK2 inhibitors in clinical development. Using standardized data from the Critical Path for Parkinson’s Unified Clinical Database, we quantified the rate of progression of the Movement Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) Part I (non-motor aspects of experiences of daily living) in 158 PD participants who were carriers and 598 PD participants who were non-carriers of at least one of three different LRRK2 gene mutations (G2019S, R1441C/G, R1628P).

Age and disease duration were found to predict baseline disease severity, while presence of at least one of these three LRRK2 mutations was a predictor of the rate of MDS-UPDRS Part I progression. The estimated progression rate in MDS-UPDRS Part I was 0.648 (95% confidence interval: 0.544, 0.739) points per year in non-carriers of a LRRK2 mutation and 0.259 (95% confidence interval: 0.217, 0.295) points per year in carriers of a LRRK2 mutation. This analysis demonstrates that the rate of progression based on MDS-UPDRS Part I is approximately 60% lower in carriers as compared to non-carriers of LRRK2 gene mutations.

Introduction

Parkinson’s disease (PD) is the fastest growing and the second most common progressive neurodegenerative disease, involving several neurotransmitter pathways within the central nervous system\(^1\). Motor deficits of PD, such as bradykinesia and rigidity, result from loss of dopaminergic
neurons in the substantia nigra. Existing treatments that supplement dopamine largely improve these symptoms for a short period of time but have no effect on disease progression\textsuperscript{2}. However, PD is also characterized by non-motor symptoms (NMS) such as hyposmia, sleep disorders (REM behavior disorder (RBD)), depression, constipation, cognitive and behavioral problems that are postulated to be linked to neurotransmitter deficits\textsuperscript{3} and are very burdensome to participants\textsuperscript{4}. Some NMS begin in the prodromal phase several years prior to the onset of motor features and continue to develop throughout the disease continuum, with dementia, hallucinations and autonomic dysfunction becoming more prominent in the later stages of the disease. The temporal clinical presentation of NMS and their rate of progression can vary among participants\textsuperscript{3,5}. Emerging evidence supports a more central role of NMS in disease pathogenesis and onset\textsuperscript{6}.

Genetic forms of PD are rare, but of major importance for understanding the pathophysiology of PD\textsuperscript{7}. Mutations associated with leucine-rich repeat kinase 2 (LRRK2) gene are one of the most frequent known contributing factors to late-onset PD, with mutation frequency ranging from 2 to 40\%\textsuperscript{8-11}. Although the mechanism relating LRRK2 mutations to PD is still uncertain, several mutations in the LRRK2 gene have been identified, with the most common deleterious variant being the G2019S mutation\textsuperscript{12}. Recent studies indicate PD participants who carry LRRK2 mutations show an unexpectedly slower rate of motor disease progression than idiopathic PD (iPD) cases\textsuperscript{13,14}. In addition, although Rachel Saunders-Pullman \textit{et al.} did not find a significant difference in the change in Montreal Cognitive Assessment (MoCA) score, the direction of change is in support of a better cognitive course in individuals carrying the \textit{LRRK2} mutation\textsuperscript{13}. However, data on progression of NMS in LRRK2-PD cases are lacking.

Using standardized data from the Parkinson’s Progression Marker Initiative (PPMI) observational longitudinal cohort, we quantified the differences in progression of the Movement
Disorder Society-sponsored revision of the Unified Parkinson’s Disease Rating Scale Part I (MDS-UPDRS Part I, non-motor aspects of experiences of daily living) in PD participants with and without LRRK2 gene mutations.

The MDS-UPDRS was developed as a four-part scale to evaluate various aspects of Parkinson’s disease, including non-motor and motor experiences of daily living and motor complications. Part I of the MDS-UPDRS (referred to hereafter as MDS-UPDRS1) consists of 13 items that are typically viewed as a measure of non-motor functional impairment and is used to describe non-motor PD disease progression in this manuscript. In this analysis, we focused on the three of the most common LRRK2 mutations: G2019S, R1441C/G and R1628P. Throughout the manuscript, participants with at least one of these mutations will be referred to as LRRK2 mutation carriers.

The specific aims of the current analysis were to 1) develop a longitudinal disease progression model for NMS of PD using data from PPMI, and 2) identify relevant participant characteristics (e.g., LRRK2 mutation status, age, disease duration, etc.) associated with temporal changes in NMS. In addition, this analysis looks to expand our overall understanding of progression of PD symptoms based on a quantitative approach. As part of these aims, relevant participant characteristics and LRRK2 mutations were evaluated as predictors of baseline severity and longitudinal change of non-motor score as represented by the MDS-UPDRS1.

The current analysis was carried out in collaboration with the Critical Path for Parkinson’s CPP Consortium, a public-private partnership of the Critical Path Institute co-funded by Parkinson’s United Kingdom and industry sponsors. The source of data in the present study was derived from the CPP Unified Clinical Database (referred to hereafter as the CPP database). The
outcome of this effort aligns with the vision of CPP, which is to create quantitative tools and accelerate drug development in PD.

**Methods**

**Data**

Participant-level, longitudinal clinical data were extracted from the CPP database and used to build the analysis dataset. The CPP database is a data platform designed to curate, standardize and make data available to CPP members to generate solutions that expedite the development of treatments for PD. The data in the CPP database were integrated using open access consensus data standards published by the Clinical Data Interchange Standards Consortium (CDISC). These standards included the foundational Study Data Tabulation Model and the Therapeutic-Area User Guide version 1.0 for PD. The CPP database consists of patient level item level data from both PD observational cohorts and clinical trials. The most comprehensive genetic data is available from PPMI.

The PPMI study from the CPP database was investigated in this analysis. PPMI is an international, multicenter, prospective study designed to identify clinical, imaging and biologic markers of PD progression (National Clinical Trials identifier NCT01141023). PPMI enrolled patients with early untreated (De Novo) PD and healthy controls between 2010 and 2013. In 2014, the study was expanded to include genetic cohorts with PD as well as non-manifesting carriers of mutations in SNCA, LRRK2, and GBA. A further expansion of PPMI launched in 2014 with a Genetic registry cohort which consists of subjects with and without PD who have a genetic mutation in LRRK2, GBA, or SNCA or a first-degree relative with a LRRK2, GBA, or SNCA mutation.
PPMI has longitudinal data for non-motor scores as well as LRRK2 genetic status at the subject level\textsuperscript{18}; the genetic PD cohorts were recruited across disease stages. The target population for the present analysis is focused on LRRK2 mutation carrier’s vs iPD participants in manifest PD. Analysis of data from PD subjects in three cohorts from the PPMI study were included in the present analysis: 1) De Novo PD Cohort, which was comprised of subjects diagnosed with PD within two years or less and with subjects who did not initiate any PD treatment for the first 6 months from baseline (379 subjects), 2) Genetic PD Cohort, which was comprised of PD subjects with a genetic LRRK2 mutation (209 subjects), and 3) Genetic PD Registry Cohort, which was comprised of PD subjects with a genetic LRRK2 mutation and who were evaluated at less frequent intervals to augment and broaden the follow-up duration (167 subjects). Evaluation of GBA and SNCA carriers was not conducted in this analysis; relatives or nonmanifest gene carriers were not included.

The PPMI study evaluated a total of six different LRRK2 variants (R1441G, R1441C, R1628P/H, Y1699C, G2019S, G2385R): (PPMI website, Participant Genetic Status for Selected PD associated variants and Genetic Status for Selected PD Associated Variants Methods). The three LRRK2 mutations evaluated in this analysis are the most common LRRK2 mutations. The majority of LRRK2 variants in PPMI belong to G2019S given that enrollment was focused on the Ashkenazi Jewish community\textsuperscript{19}.

PPMI data were downloaded from the CPP database in January 2019. The CPP database consists of cohorts and genetics that were initiated many years ago. Disease duration for LRRK2 carriers mean (range) BL PD duration is 1.91 (0, 15.7) years and for noncarriers is 0.42 (0, 29.5) years. Disease duration is defined as time from onset of clinically confirmed motor diagnosis of PD.
The International Parkinson and Movement Disorder Society revision to the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is a Parkinson's disease rating scale that includes examiner and patient/caregiver input. It is composed of four parts: Part I - Non-Motor Aspects of Experiences of Daily Living; Part II - Motor Aspects of Experiences of Daily Living; Part III - Motor Examination; Part IV - Motor Complications. MDS-UPDRS Part I scale consists of 13 items (Supplementary Table 1) covering a range of non-motor symptom domains. The maximum score for Part I (Parts IA and IB) is 52 points (13 items x the maximum score 4). At the time of the designing the research, MDS-UPDRS\textsubscript{1} data from PPMI were available. Data from the CAMPAIGN study were not evaluated in this study given that Part I score was measured using the legacy UPDRS measure and could not be reliably converted to MDS-UPDRS\textsubscript{1}.\textsuperscript{16} Therefore, only the PPMI database that used MDS-UPDRS for capturing Part I scores was used in the present analysis. Individual MDS-UPDRS\textsubscript{1} values were scaled based on the maximum observed MDS-UPDRS\textsubscript{1} score in the dataset and modeled as a continuous variable; values were bounded by 0 and 1.

**Model-building process**

Beta regression, implemented within the nonlinear mixed-effects modeling framework as described in Ahamadi *et al.*\textsuperscript{14} was used to develop the disease progression model for NMS. The selection of the final disease progression model and model validation followed the steps described in Ahamadi *et al.*\textsuperscript{14} The NONMEM Laplacian estimation method was used for optimization to handle the second derivative of the inter-individual variability parameters. Pearl Speak NONMEM (PsN)\textsuperscript{20} and R (R-project, www.r-project.org) software packages were used for the exploratory analysis and post-processing of NONMEM outputs. As MDS-UPDRS\textsubscript{1} is a bounded scale, beta regression was used to address the challenges associated with this type of bounded data, which are
typically heteroscedastic, displaying more variability around the mean and less variability around
the lower and upper boundary of the scale. The use of beta regression to characterize bounded
measures of cognition have been described previously.

A longitudinal model without covariates was first developed as a base model. Once the
robustness of the base model was established, a series of exploratory covariate analyses were
performed to assess the correlation between covariates and the correlation between covariates and
baseline disease severity. Results from exploratory covariate analyses were combined with prior
knowledge of potential predictors of PD progression to select the combination of parameters and
covariates to undergo formal assessment. Covariates tested for inclusion in the model included
demographic factors (e.g., age, gender, and body weight, etc.), disease duration at study entry,
years of education, LRRK2 mutation, and use of dopaminergic medication (e.g.,
levodopa/dopamine agonists). Dopaminergic medication classification was binary categorization
not quantified in this analysis. Selection of statistically significant covariates that impact key
disease progression model parameters (e.g., baseline and slope) followed the previously described
stepwise covariate selection procedure (SCM). Briefly, the stepwise covariate selection
procedure as implemented in PSN was used to confirm findings from exploratory analyses. The
SCM procedure involved stepwise testing of linear and nonlinear relationships in a forward
inclusion (change in objective function value, DOFV, of 6.63, \(P < 0.01\), chi-squared with 1 degree
of freedom, DF) and backward exclusion (DOFV of 10.8, \(P < 0.001\), chi-squared with 1 DF)
procedure. As noted above, a relatively stringent significance level was used for covariate testing
\((P < 0.01 \text{ in the forward step, } P < 0.001 \text{ in the backward step})\) to mitigate the likelihood of false
positives given that multiple hypothesis testing was applied during the covariate search.
Model Evaluation

Assessment of model adequacy, as well as decisions to increase model complexity, was guided by goodness-of-fit criteria, which included evaluation of objective function value (OFV) and Bayesian information criterion (BIC; defined as OFV + np*Ln(N), where np is the total number of parameters in the model, and N is the number of data observations). Visual inspection of diagnostic scatter plots, such as observed vs. predicted scores, plausibility of parameter estimates, and precision of parameter estimates, was used to select the final model. Robustness of the model parameter estimates was assessed by means of non-parametric bootstrap evaluation. The disease progression parameters were estimated repeatedly by fitting the final model to 1,000 bootstrap datasets sampled from the original dataset with replacement. The median values and 95% confidence intervals (CIs) of the parameter estimates from these 1,000 bootstrap datasets were compared with the point estimates from the original dataset.

Results

Data summary

The analysis dataset was comprised of three cohorts from the PPMI study: 1) De Novo PD Cohort, which included participants diagnosed with PD within two years at baseline and who did not initiate any PD treatment for the first six months from baseline (423 participants); 2) Genetic PD Cohort, which was comprised of PD participants with a mutation in genes that include LRRK2, glucocerebrosidase (GBA), or alpha synuclein (SNCA) (257 participants); and 3) Genetic PD Registry Cohort, which is comprised of PD participants with a genetic mutation in LRRK2GBA, or SNCA, and who were evaluated at less frequent intervals to augment and broaden the follow-up of PD participants (202 participants). The mean follow-up time duration for the PD, Genetic
PD, and Genetic PD registry cohorts was 60, 27, and 13 months, respectively, with an overall mean follow-up duration for all subjects of 40 months (Table 1). As described in the Methods section, multivariate analysis was conducted to account for the effect of disease duration on baseline and slope. The following LRRK2 variants were available in the analysis dataset: G2019S (rs34637584), R1441C/G (rs33939927), R1628P (rs33949390) and non-coding variant (rs76904798). Note that for variant rs33939927, only the C>G (R1441G) and C>T (R1441C) alleles were represented in the dataset, so the mutation is referred to as R1441C/G. A study performed by Li et al.\textsuperscript{25} showed that the PD risk allele rs76904798 at the LRRK2 locus is associated with increased expression of LRRK2 in monocytes (p = 2.93 × 10\textsuperscript{-8}), but not in dorsolateral prefrontal cortex (p = 0.98) and hence not significantly associated with PD risk; therefore, participants carrying the non-coding mutation of LRRK2 (rs76904798) were not included in the analysis. Only PD participants carrying G2019S (rs34637584), R1441C/G (rs33939927) or R1628P (rs33949390) mutation were defined as LRRK2 participants. Finally, participants with GBA mutations were excluded from the analysis to avoid any potential interaction between GBA and LRRK2 and to ensure that the non-LRRK2 cases were more representative of iPD. A summary of the demographic and participant characteristics for the pooled analysis dataset is presented in Table 1.

**Model development**

**Base Model**

The generalized Gompertz model\textsuperscript{26}, as defined in Equation 1, described the longitudinal MDS-UPDRS\textsubscript{1} data adequately.
Equation 1: \[
\frac{d\text{Score}_i}{dt} = r_i \text{Score}_i \left[ \ln \left( \frac{\text{max}(\text{Score})}{\text{Score}_i} \right) \right]^\gamma
\]

where, \( r_i \) is the intrinsic rate of progression, \( \text{Score}_i \) is MDS-UPDRS1, score for individual \( i \), \( \gamma \) represents the shape/steepness parameter controlling the inflection point and \( \text{max} (\text{Score}) \).

Supplementary Table S2 presents a summary of additional logistic models evaluated leading to selection of the Gompertz model as the best structural base model. Evaluation of random effect models on slope and baseline parameters led to the estimation of correlated inter-individual variabilities on baseline and slope. The base model was stable upon perturbation of initial parameter estimates and had a low condition number (16.2); also, goodness-of-fit plots showed population and individual predicted scores were estimated without bias (Supplementary Figure S1).

**Covariate Analysis**

Figure 1 illustrates the correlation between baseline severity and all covariates considered for formal testing. Disease duration had the highest correlation with baseline (correlation coefficient of 0.337), indicating that PD participants with longer disease duration are expected to have high non-motor disease severity. The observed data suggest a minor negative correlation (-0.126) between gender and baseline, translating into females having slightly higher non-motor disease severity than males. Minor correlation was also seen between age, LRRK2 mutation and dopaminergic medications and baseline; gender was highly correlated with baseline body weight. Therefore, these two covariates were not tested simultaneously. Additional exploratory evaluations can be found in Supplementary Figure S2. Results from the covariate analyses suggest an increase of baseline disease severity as a function of increasing disease duration. Goodness-of-fit plots confirmed the adequacy of the final model to describe both total population and individual study
populations without bias (Supplementary Figure S1). Supplementary Table S3 presents a full list of significant and non-significant covariates together with their estimates and P-values.

**Final model**

Age was not selected as a statistically significant covariate based on the selection criteria imposed on the SCM. However, with the progression of neurodegeneration and advancing of PD, NMS such as cognitive impairment, autonomic dysfunction and sleep disorders become severe with age and are important determinants of quality of life. Moreover, a weak correlation between age and baseline score was observed in our dataset (Figure 1). Therefore, age was included in the final covariate model as a clinically relevant covariate during model refinement. Additional improvements to the covariate model were explored, including reassessment of the covariance structure for random effects for model improvement. The covariate model utilizing the generalized Gompertz model with age and disease duration on baseline and LRRK2 mutation on slope was selected as the final model. The condition number (calculated as the ratio of the largest eigenvalue to the smallest eigenvalue) for the final covariate model was 16.3. To assess the robustness, the final model was fit to 1,000 bootstrap replicate datasets to evaluate its stability and performance. Among the 1,000 runs, only 3 (0.3%) failed. Consistency between parameter estimates from the final model along with 95% CIs obtained from successfully converged bootstrap runs are shown in Table 2. For all model parameters, the median of bootstrap estimates was very close to the final model estimates. Precision of parameter estimates (described by %RSE or CI) was also comparable for all parameters with the exception of the parameter quantifying the effect of LRRK2 mutation on disease progression rate. The estimate for the effect of LRRK2 mutation on disease progression had greater bootstrap uncertainty compared to the uncertainty reported in the final model. This could partly be due to the smaller proportion of subjects with
LRRK2 mutation. Additional plots comparing the distribution of parameters from bootstrap estimates and the final model are presented in Supplementary Figure S3.

**Simulation assessing the impact of selected covariates**

The following simulations were conducted to quantify the impact of significant covariates identified in the covariate analysis: (1) age on baseline disease score, (2) disease duration on baseline disease score and (3) LRRK2 mutation on disease progression rate. For each covariate category, 1,000 virtual participants were generated using parameter uncertainty obtained from bootstrap runs of the final model. In each scenario, all other factors (except the covariate category of interest) were kept constant.

*Covariate impacting progression rate*

Figure 2 demonstrates a slower disease progression of participants with LRRK2 mutation compared to participants without LRRK2 mutation as expected from the findings of the covariate analysis. The estimated progression rate in non-motor score among participants without LRRK2 mutation was 0.648 (95% confidence interval: 0.544, 0.739) points per year, while it is estimated at 0.259 (95% confidence interval: 0.217, 0.295) points per year for participants with LRRK2 mutation, corresponding to a ~60% slower progression rate.

*Covariates impacting baseline*

Figure 3 shows simulations that illustrate the impact of covariates (age and disease duration) on baseline severity. An increase in age from 32 to 63 years is associated with an approximately 10% increase in baseline non-motor score (Figure 3, left panel). An increase in disease duration from one to five years is associated with an approximately 20% increase in baseline non-motor score (Figure 3, right panel).
Impact of disease duration on assessing impact of LRRK2 mutation on disease progression

One of the challenges in developing a comprehensive disease-progression model in PD is the accurate handling of the wide ranges of disease duration of PD participants in observational studies. Participants with severe PD may progress slower and those in early stage PD may progress faster. This imbalance in the rate of disease progression between participants at different stages of PD could affect our understanding of the difference in the progression rate between PD participants with or without LRRK2 mutation. However, the disease progression model developed in the current analyses suggests that disease duration at enrollment impacts baseline disease score, but not the disease progression rate at follow up. Simulations were performed using bootstrap parameter uncertainty to quantify the disease progression rate of participants with and without LRRK2 mutation. Figure 4 presents simulated rates of disease progression at different disease durations. Overall, slower progression is observed in participants with LRRK2 mutation compared with those without, regardless of the time since diagnosis.

Discussion

The present study describes quantitatively a disease progression model for NMS of PD based on observational data collected in the PPMI observational longitudinal cohort. Age and disease duration were found to be significant covariates on baseline MDS-UPDRS1 such that baseline score increased with increase in age and disease duration. LRRK2 mutation status was the only significant covariate on disease progression rate, indicating a slower rate of disease progression in the LRRK2 mutation cohort as compared to participants not carrying a LRRK2 mutation. Motor features of Parkinsonism associated with Lewy bodies and loss of dopaminergic neurons in the substantia nigra have been defined as hallmarks of PD. In recent years, however,
PD has become recognized as a heterogeneous disease, with clinically significant non-motor features resulting from a complicated interplay of genetic and environmental factors affecting numerous fundamental cellular processes in different brain regions and the periphery. Recent efforts in developing disease-modifying therapies have resulted in the identification of several genetically validated targets such as LRRK2. Several clinical trials are currently underway to test the hypothesis that inhibition of LRRK2 can slow disease progression. At present more than 100 mutations in the LRRK2 gene have been identified. The frequency of mutations varies in different geographical regions and in different ethnic populations. Therefore, it is important to elucidate the role of different genetic variants on PD outcome measures of disability to support multisite global clinical trials. The present study focused on evaluation of PD progression of non-motor features in LRRK2 mutation carriers, given their potential importance as clinical outcomes in such trials.

**Base Model**

Similar to our previous work, beta regression (i.e., combination of a logistic model and beta-distributed residual variability) has been used to characterize the longitudinal progression of MDS-UPDRS in PD participants. The data were well described by the generalized Gompertz model comprising of three core elements: baseline, slope and shape parameters. These parameters provided flexibility to describe both the linear and nonlinear portions of non-motor disease progression. In our previous analysis, the progression rate of motor symptoms was estimated to be ~0.284 points/month, while herein it is estimated at ~ 0.0537 points/month for non-motor symptoms. These estimations are within the range of the estimated progression rate reported by Holden et al. using the PPMI study. In this study it was reported that MDS-UPDRS total score increased an estimated 4.7 points per year, Part I scores increased 0.92 points per year, Part II
scores increased 0.99 points per year, and Part III scores increased 2.4 points per year. Additional investigations have also reported longitudinal model-based analyses using PPMI data\textsuperscript{33,34}.

**Difference in motor and non-motor progression rates**

The difference between motor and non-motor progression rates observed in our analyses is consistent with the clinical expectation\textsuperscript{1} that motor symptoms progress relatively rapidly after diagnosis. Figure 5 shows model-based predictions for motor and nonmotor progression up to 10 years of follow-up. It is important to note that simulations of study designs carried out for up to two-years in duration are more relevant for trial design considerations.

**Covariate Analysis**

The covariate analysis identified age and disease duration as predictors of baseline MDS-UPDRS\textsubscript{1}. LRRK2 mutations were identified as predictors of the non-motor disease progression rate. The increase of baseline disease severity as a function of increasing disease duration is consistent with results reported by Liu et al.\textsuperscript{35} on the impact of NMS on quality of life in participants with PD. Their analysis found disease duration and severity as major predictors of NMS. Age was tested as a clinically relevant covariate and found to be an important determinant of non-motor baseline severity. The power coefficient of the age effect was estimated to be 0.00342, indicating that older PD participants have higher disease severity than younger PD participants. The correlation between age and non-motor score in the literature has produced mixed results, with both correlation\textsuperscript{18} and non-correlation\textsuperscript{36} being reported. It is important to note that our results agree with the fact that NMS, such as cognitive impairment, autonomic dysfunction and sleep disorder, become increasingly severe with advanced age and are the main determinants of quality of life. The slope coefficient of the disease duration effect indicates an increase of baseline
disease severity with increasing disease duration. This correlation between burden of NMS and disease duration has also been reported in other studies\textsuperscript{37,38}. Disease duration was not found to be directly correlated to the rate of non-motor progression, which is consistent with the findings from Simuni et al\textsuperscript{18}. Our analysis did not identify a correlation between non-motor score and class of dopaminergic therapy, in agreement with the hypothesis that NMS are mostly driven by non-dopaminergic pathways\textsuperscript{3,39}. Interestingly, in their multivariate analysis, Simuni et al\textsuperscript{18} reported that higher baseline non-motor score was associated with female sex (p=0.008). Our analysis did not identify a correlation between gender and baseline of non-motor score. Other covariates tested, such as weight and years of education, did not have a significant impact on non-motor baseline severity or progression. It is worth noting that comorbid conditions may impact baseline or disease progression but were not evaluated as covariates in the current analysis.

Non-motor progression in PD participants with LRRK2 mutation was found to be slower than progression in PD participants without LRRK2 mutation. The slower motor progression in PD participants with LRRK2 mutation has been reported in the literature\textsuperscript{13,14}. Saunders-Pullman et al\textsuperscript{13} also reported slow progression of non-motor score for PD participants with LRRK2 G2019S mutation. Furthermore, slower progression in participants with LRRK2 G2019S was reported for total UPDRS, UPDRS I, UPDRS III, posture, gait, and balance scores\textsuperscript{13}. However, one four-year longitudinal study of LRRK2 mutation carriers in an Asian population reported a faster rate of progression of both motor and non-motor symptoms as assessed by modified Hoehn & Yahr measures\textsuperscript{40}. The reasons for the apparent differences as compared to our results might include different geographic populations (Singapore vs US), different genetic variants (most common Asian population variants are G2385R, R1628P and S1647T), or different outcome measures (Hoehn & Yahr score vs MDS-UPDRS\textsubscript{1}). In this analysis, we identified a slower
progression rate of non-motor symptoms in PD participants with LRRK2 mutation compared to those without mutation in a LRRK2 carrier population comprised of a mixture of LRRK2 mutations: G2019S (rs34637584), R1441C/G (rs33939927) and R1628P (rs33949390). Findings from our previous analysis\textsuperscript{14} combined with the present analysis indicate that progression of both motor and non-motor symptoms in PD participants with LRRK2 mutation is slower than PD participants without LRRK2 mutation.

Findings from the current analysis have the potential to impact clinical trial design for future agents that may target only participants with LRRK2 mutations, who have slower disease progression relative to iPD participants. For the purpose of trial design, a two-year duration is most relevant, and based on 1,000 model simulations, the mean MDS-UPDRS\textsubscript{1} at the end of two years for the typical participant (63 year old male with a baseline PD duration of 6 months) is predicted to be 6.45 and 6.23 in iPD and LRRK2 PD participants, respectively. While differences in mean MDS-UPDRS\textsubscript{1} between iPD and LRRK2-PD participants increase beyond two years, uncertainty in the model predictions are also higher. The analysis suggests that within the constraints of a clinical trial, the difference in disease progression may not be meaningful and enriching clinical trials with LRRK2-PD participants will not allow a smaller sample size. It is also worth noting that the magnitude of drug effect in these two populations may be different and will also impact the sample size and trial design. Thus, the model may be used via simulation to optimize clinical trial design to detect treatment effects by accounting for the impact of disease progression. Moreover, Di Maio \textit{et al.}\textsuperscript{41} have suggested that LRRK2 may play a role in iPD, meaning that the therapeutics targeting LRRK2 may not need to be limited to LRRK2 mutation carriers, and may potentially be beneficial for a wider population of the PD community. Given this
information, simulations can be conducted to understand the power of detecting treatment effects with varying proportions of iPD and LRRK2 mutation individuals enrolled in a clinical trial.

It is worth noting that median disease duration at study entry was different across various PPMI cohorts, where disease duration was shorter (8 months) for iPD participants compared to participants with a LRRK2 mutation (23.5 months). While multivariate analysis was conducted to account for the effect of disease duration on baseline and slope, disease duration was only found to be a significant covariate impacting baseline disease severity. Nevertheless, confounding between disease duration and LRRK2 mutation cannot be ruled out. Cilia et al. have also found that PD participants with LRRK2 mutations are more likely to be women. Based on the PPMI database, 26.5% of women had LRRK2 mutations compared to only 16.8% of men. Based on the covariate analysis, gender was not found to be a covariate on baseline or rate of disease progression. Future investigations will be important to expand the findings of this present study by evaluating the fate of LRRK2 nonmanifest carriers that are at the prodromal stage or present with RBD as well as to investigate the impact of other leading candidate genes such as GBA and SNCA in PPMI and other natural history studies in diverse populations.

We acknowledge that our analysis has some limitations. First, the current analysis uses data from observational studies that may not reflect placebo-controlled clinical trial data from randomized trials. The high proportion of genetically defined subjects in our study may not reflect true clinical trial populations comprised of iPD subjects. Furthermore, we did not evaluate all NMS of PD (e.g., sexual function, olfaction, or restless leg syndrome) as these items are not included in the MDS-UPDRS. Finally, some non-motor symptoms (e.g., psychiatric symptoms, sleep) are known to be impacted by medication use. Our analysis, which was limited to examining non-time varying levodopa/dopamine agonist use, was not comprehensive enough to evaluate the
effects of class-specific PD medication use, dopaminergic medication dose and other concomitant medications on non-motor progression. Nevertheless, describing the quantitative differences of non-motor disease progression rate in participants with LRRK2 mutations is critical in designing future trials.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

LRRK2 inhibitors are being pursued as novel therapies for PD. Motor symptoms for PD participants carrying LRRK2 mutations have been shown to progress more slowly compared to idiopathic PD. However, little has been reported on the difference in progression rate of non-motor symptoms between these two population subsets.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study addressed the following question: Do LRRK2 mutations impact progression rate of non-motor symptoms in participants with PD?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The rate of progression of non-motor symptoms in PD participants carrying LRRK2 mutations is significantly slower than participants with idiopathic PD. This study has implications to inform the efficient design of clinical trials with LRRK2-PD participants.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

An understanding of the quantitative differences of non-motor disease progression rate in LRRK2 carrying and idiopathic PD can be leveraged to inform clinical trial design for therapeutics
targeting non-motor PD symptoms. It is recommended that Clinical Trial Simulations be carried out to inform trials and estimate the power of detecting treatment effects with varying proportions of iPD and LRRK2 mutation individuals enrolled in a clinical trial.

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**Author Contributions**

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**References**


Figure Legends

**Figure 1. Correlations between baseline MDS-UPDRS1 score and selected covariates.** Correlation heatmap matrix of covariates tested in stepwise covariate modeling procedure. White boxes represent no correlation. Light red boxes represent a small positive correlation, with increasing positive correlation represented by a darker red shade. Light blue boxes represent a small negative correlation, with increasing negative correlation represented by a darker blue shade.

**Figure 2. Disease progression of participants with LRRK2 mutation compared to those without LRRK2 mutation.** Simulation showing slower progression of subject with LRRK2 mutation compared with participants without LRRK2 mutation. All virtual populations were assumed to be 63 years old with the same disease duration of 6 months; red and blue dashed lines represent medians of simulated progression rates for participants with and without LRRK2 mutations, respectively. Grey areas represent 90% CI of predictions.

**Figure 3. Impact of significant covariates impacting baseline MDS-UPDRS1.** Left panel: simulation showing non-motor baseline scores with respect to age: 32-, 65- and 88-year old participants correspond to non-motor baseline of 5.487, 6.173 and 6.687, respectively. Right panel: simulation showing ~20% increase of non-motor baseline score with increase of disease duration of 1, 5, 10, 15 and 20 years corresponding to non-motor baseline of 6.204, 7.752, 9.681, 11.6 and 13.52, respectively.
Figure 4: Simulated progression rate for MDS-UPDRS$_1$ between PD participants with or without LRRK2 mutation at different disease durations. Simulations showing disease progression of PD participants with or without LRRK2 mutation at different disease durations. Slower progression is observed in participants with LRRK2 mutation and is independent of time since diagnosis.

Figure 5. Simulated time courses of motor and non-motor progression of Parkinson’s disease based on the final disease progression model. Non-motor symptoms are defined as MDS-UPDRS$_1$ and motor symptoms as MDS-UPDRS$_2$ and MDS-UPDRS$_3$. Parameters used to simulate the motor symptoms were obtained from$^{11}$ while those of non-motor symptoms were obtained from Table 2.
Supplementary Materials

Figure S1. Goodness-of-fit plots for the final model

In the two plots of the first row, solid lines are lines of identity. In the two plots of the second row, solid lines represent zero line, while red dashed lines represent lm fits. Pearson residuals were calculated as (DV-IPRED)/SQRT(IPRED*(1-IPRED)/(1+τ)), where DV is the dependent variable MDS-UPDRS1 score, IPRED is the individual prediction, and τ the summation of the shape parameters of the beta distribution.

Abbreviations: MDS-UPDRS1 = Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I

Figure S2. Correlation between baseline MDS-UPDRS1 and covariates

A-D. Correlation between baseline and continuous covariates (age, disease duration, body weight and years of education) solid lines are linear model fits, with shaded areas representing 95% confidence intervals;

E-H. Correlation between baseline and categorical covariates (gender, concomitant medication, handedness, and race)

Abbreviations: MDS-UPDRS1 = Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I score.

Figure S3. Comparison between parameter estimates and bootstrap results

Dashed grey vertical black lines are bootstrap 2.5th, median, and 97.5th percentiles. Solid vertical red line is the original NONMEM estimate.

Abbreviations: LRRK2 = Leucine-rich repeat kinase 2, MDS-UPDRS1 = Movement Disorder Society-Unified Parkinson's Disease Rating Scale Part I score.

Table S1. Components of MDS-UPDRS Part I Score

Table S2. Base model structure

Abbreviations: OFV = objective function value; BIC = Bayesian information criterion

Table S3. Covariate modeling

Abbreviations: SCM = stepwise covariate modeling; OFV = objective function value; df = degrees of freedom;
LRRK2 = Leucine-rich repeat kinase 2
* P-value derived from the chi-square distribution (forward step acceptance level: 0.01, backward step acceptance level: 0.001). Insignificant covariates on baseline and slope include years of education, weight, concomitant medication, and gender.