Clinical and Dopamine Transporter Imaging Characteristics of Leucine Rich Repeat Kinase 2 (LRRK2) and Glucosylceramidase Beta (GBA) Parkinson's Disease Participants in the Parkinson's Progression Markers Initiative: A Cross-Sectional Study

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RESEARCH ARTICLE

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Members of the Parkinson's Progression Markers Initiative Investigation are listed in the Appendix.

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ABSTRACT: Background: There are limited data on the phenotypic and dopamine transporter (DAT) imaging characterization of the Parkinson's disease (PD) patients with leucine rich kinase 2 (*LRRK2*) and glucosylceramidase beta (*GBA*) mutations.

Objective: The objective of this study was to examine baseline clinical and DAT imaging characteristics in *GBA* and *LRRK2* mutation carriers with early PD compared with sporadic PD.

Methods: The Parkinson's Progression Markers Initiative is an ongoing observational longitudinal study that enrolled participants with sporadic PD, *LRRK2* and *GBA* PD carriers from 33 sites worldwide. All participants are assessed annually with a battery of motor and nonmotor scales, 123-I Ioflupane DAT imaging, and biologic variables.

Results: We assessed 158 *LRRK2* (89% G2019S), 80 *GBA* (89 %N370S), and 361 sporadic PD participants with the mean (standard deviation) disease duration of 2.9 (1.9), 3.1 (2.0), and 2.6 (0.6) years, respectively. When compared with sporadic PD, the *GBA* PD patients had no difference in any motor, cognitive, or autonomic features. The *LRRK2* PD patients had less motor disability and lower rapid eye movement behavior disorder questionnaire scores, but no meaningful difference in cognitive or autonomic features. Both genetic cohorts had a higher score on the impulse control disorders scale when compared with sporadic PD, but no difference in other psychiatric features. Both genetic PD cohorts had less loss of dopamine transporter on DAT imaging when compared with sporadic PD.

Conclusions: We confirm previous reports of milder phenotype associated with *LRRK2*-PD. A previously reported more aggressive phenotype in *GBA*-PD is not evident early in the disease in N370s carriers. This observation identifies a window for potential disease-modifying interventions. Longitudinal data will be essential to define the slope of progression for both genetic cohorts.

Trial Registration: ClinicalTrials.gov (NCT01141023).

Key Words: genetics; Parkinson's disease

Mutations in the leucine rich kinase 2 (*LRRK2*) and heterozygous mutations in glucosylceramidase beta (*GBA*) are the 2 most common genetic risk factors for PD, responsible for up to 10% of Parkinson's disease (PD) cases globally and up to 30% to 40% in certain ethnic subgroups and cases with familial disease.[1,2] There is a rapidly growing number of novel therapeutics targeting specifically underlying biology associated with *GBA* and *LRRK2* mutations, with some of these already being tested in early phase clinical trials.[3] There is also accumulating evidence regarding difference in clinical manifestations and rate of progression of *GBA* and *LRRK2* PD. Current data points to a higher burden of nonmotor manifestations specifically cognitive dysfunction, rapid eye movement sleep behavior disorder (RBD), hyposmia, and more rapid disease progression associated with *GBA* PD.[4-13] On the contrary, *LRRK2* PD is reported to be associated with less risk of cognitive dysfunction, RBD, hyposmia, and slower rate of motor progression.[12,14-19] There are some reports of higher prevalence of psychiatric symptoms associated with *LRRK2* PD, although the data are not consistent.[20,21] Although there is a growing body of literature examining motor, nonmotor, and imaging characteristics of *LRRK2* and *GBA* PD carriers, there are still limited data from large, controlled, prospective longitudinal cohort studies comparing early-stage *GBA* and *LRRK2* PD to sporadic PD (sPD) specifically focusing on nonmotor manifestations as well as allowing comparisons between *GBA* and *LRRK2* PD cohorts.[12,13] The Parkinson's Progression Markers Initiative (PPMI) is an ongoing observational, international, multicenter cohort study aimed at identifying blood-based, genetic, spinal fluid and imaging biomarkers of PD progression with longitudinal follow-up in a large cohort. PPMI enrolled patients with early untreated (de novo) PD (n = 423) as well as similar age and gender healthy controls (n = 196) between June 2010 and April 2013. The study was expanded in 2013 to include genetic cohorts with PD associated with α-synuclein gene, *LRRK2*, or *GBA* mutations. Once enrolled, all participants undergo the same scope of annual assessments thus providing a unique opportunity to compare different cohorts using the same scope of activities.

The aim of this analysis was to systematically evaluate the baseline motor and nonmotor clinical and dopamine transporter (DAT) 123-I ioflupane single photon emission computed tomography imaging (SPECT) characteristics of *GBA* and *LRRK2* PD patients compared with sPD participants enrolled in PPMI and to assess the differences between the 2 PD genetic cohorts. We hypothesized that *GBA* PD will have more severe and *LRRK2* PD milder PD motor and nonmotor manifestations when compared with sPD.

Methods

Study Design

Data used in the preparation of this manuscript were obtained from the PPMI database (www.ppmi-info.org/data). The aims and methodology of the study have been published elsewhere.[22,23] The study protocol and manuals are available at www.ppmi-info.org/study-design.

Participants

The data used for this article include the analysis of the baseline dataset for *LRRK2* and *GBA* PD patients enrolled between January 2014 and May 2019 from 33 participating sites worldwide. PD *LRRK2* and *GBA* mutation carriers cohort enrolled male or female participants aged 18 or older with the diagnosis of PD based on established diagnostic criteria,[24] a disease duration less than 7 years at screening, Hoehn and Yahr stage less than 4, and *LRRK2* or *GBA* mutation confirmed by the genetic core. Participants were excluded if they had conditions that precluded safe performance of lumbar puncture. The sPD cohort recruited at baseline newly diagnosed, untreated PD patients who were aged 30 or older and had a disease duration less than 2 years at baseline and Hoehn and Yahr stage ≤2.[23] The sPD cohort recruitment was completed between June 2010 and April 2013. Of note, genetic PD participants were not required to be PD medication naïve at recruitment and were allowed to have longer disease duration, both criteria driven by the lower prevalence of genetic PD and the feasibility of recruitment. Considering the difference in the inclusion criteria for genetic versus sPD cohorts and the corresponding difference in baseline disease duration, we used data from the year 2 visit for the sPD cohort. The recruitment of the genetic PD cohort was done via participating sites (existing databases) and via a centralized recruitment initiative, described previously, specifically targeting PD patients of Ashkenazi Jewish (AJ) descent.[25] The study was approved by the institutional review board at each site, and the participants provided written informed consent. Data were downloaded July 1, 2019.

Genetic Testing

Genetic testing for the *LRRK2* and *GBA* genes was performed either at the site or through a central recruitment initiative via a Clinical Laboratory Improvement Amendments (CLIA) or other certified testing laboratory. The participants enrolled in the *GBA* or *LRRK2* PD cohort were notified of their genetic testing results and received genetic counseling by phone or in person by certified genetic counselors or qualified site personnel. The *LRRK2* genetic testing included G2019S and R1441G/C, N1437H mutations (in a subset of participants). *GBA* genetic testing included N370S in all, and L483P, L444P, IVS2 + 1, and 84GG mutations (in a subset of participants). Dual mutation carriers for both *LRRK2* and *GBA* were excluded from this analysis (N = 3).

This initial genetic testing was not performed in the sPD participants; however, other types of genetic research data were obtained from all PPMI participants, allowing for the identification and exclusion of these mutations in the sPD participants. Genome-wide single nucleotide polymorphisms data, whole-exome sequencing, and whole-genome sequencing data were downloaded from Laboratory of Neuroimaging (LONI) (https://ida.loni.usc.edu/); more information about all genetic project methods is available at LONI. The genetic status of 98.4% of the sPD participants was determined using more than one genetic platform. Selected mutations were extracted from all genetic data and compared within participants to create a final consensus list of participants with mutations in *GBA* or *LRRK2*. A total of 17 participants recruited into the sPD cohort were identified to have one of the aforementioned *GBA* or *LRRK2* mutations and were excluded from the analysis.

Study Outcomes

All participants enrolled into PPMI undergo the PPMI standard test battery of assessments described in detail previously.[7,8] Clinical battery includes the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) that is assessed in the medications *on* and *off* states once the participants start dopaminergic therapy; for the purpose of this analysis, we included MDS-UPDRS part III *off* scores. Other assessments include the Montreal Cognitive Assessment (MoCA) for the evaluation of global cognitive abilities, a standardized cognitive assessment battery that includes test of 5 cognitive domains, the 15-item Geriatric Depression Scale, the Scale for Outcomes for PD–autonomic function, the State and Trait Anxiety Scale, the modified Schwab and England Activities of Daily Living Scale, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), the Epworth Sleepiness Scale, the Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire (RBDSQ), and the University of Pennsylvania Smell Identification Test. Other measures include basic demographic variables, utilization of dopaminergic therapy as measured by levodopa equivalence dose (LED),[26] and utilization of psychotropic medications presented categorically (yes/no). All participants are expected to undergo DAT SPECT to assess DAT binding analyzed according to the PPMI imaging technical operations manual (http://ppmi-info.org/).[8] All participants have quantitative analysis using previously described methods to determine the minimum putamen specific binding ratio (SBR).[23] The PPMI also collects an array of cerebrospinal fluid biomarkers, but these measures are currently available only for a small subset of participants in the genetic cohort (as they are processed in batches) and as such were not included in this report.

Statistical Methods

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Chi-squared and *t* tests (and Wilcoxon rank-sum tests where appropriate) were conducted to compare baseline demographics across groups at a significance level of 0.05. Linear and logistic regression models were used to compare motor, cognitive, psychiatric, and DAT imaging characteristics across groups; all such models included gender and disease duration as covariates. To account for multiple comparisons reported here, we applied a family-wise error rate to each set of analyses. Specifically, a Bonferroni correction, computed as 0.05/number of hypotheses tested per table, was applied to Tables 2–5, resulting in adjusted significance levels of 0.05/51 = 0.001 for Table 2, 0.05/30 = 0.0017 for Tables 3 and 4, and 0.05/12 = 0.0042 for Table 5. In addition, to ensure that the study conclusions were not being influenced by participants with outlying disease duration values, sensitivity analyses were conducted on a reduced sample that restricted sPD disease duration to 2 to 4 years and 0 to 6 years for *GBA* and *LRRK2* PD.

Results

GBA PD Versus sPD

A total of 80 *GBA* PD patients and 361 sPD participants were included in the analysis. Baseline demographics, PD family history, and type of genetic mutation (for the *GBA* PD cohort) are presented in Table 1. When compared with the sPD participants, *GBA* PD patients were more likely to be women. There was no difference in age, education, ethnicity, race, age of onset, or the percent of first-degree relatives with PD between the 2 cohorts. A majority (89%) of the *GBA* PD patients carried N370S, consistent with the AJ targeted recruitment strategy. Key PD clinical characteristics of the cohorts are summarized in Table 2. There was no difference in the MDS-UPDRS total scores or part I, II, III, or IV subscores. There was no difference in University of Pennsylvania Smell Identification Test (hyposmia) and autonomic function as measured by Scale for Outcomes for PD–Autonomic Function Scale. Assessment of the cognitive characteristics of the participants revealed no difference in the MoCA score (Table 2) or detailed neurocognitive battery between

TABLE 1. Demographics and PD characteristics

Variable	*GBA* PD	*LRRK2* PD	sPD
	BL Visit, N = 80	BL Visit, N = 158	Year 2 Visit, N = 361
Age, mean (SD)	62.7 (9.9)	63.8 (9.2)	63.8 (9.7)
Sex, male, n (%)	43 (53.8)[a]	76 (48.1)[a]	238 (65.9)
Education, <13 y, n (%)	12 (15.0)	35 (22.2)	62 (17.2)
Ethnicity, Hispanic/Latino, n (%)	1 (1.3)	39 (24.7)[a,b]	8 (2.2)
Race, n (%)			
White	76 (95.0)	139 (88.5)	332 (92.0)
Missing	0	1	0
Family history of PD, n (%)			
First degree	18 (22.8)	72 (47.1)[a,b]	47 (13.1)
Second degree	11 (13.9)	25 (16.3)	42 (11.7)
None	50 (63.3)	56 (36.6)	271 (75.3)
Missing	1	5	1
Genetic mutation, n (%)			
G2019S	0 (0.0)	140 (88.6)	—
R1441C	0 (0.0)	1 (0.6)	—
R1441G	0 (0.0)	16 (10.1)	—
N1437H	0 (0.0)	1 (0.6)	—
N370S (c. 1226A>G)	71 (88.8)	0 (0.0)	—
L483P or L444P (c.1448T > C)	6 (7.5)	0 (0.0)	—
84GG (c.84_85insG)	3 (3.8)	0 (0.0)	—
Disease duration, y			
Mean (SD)	3.1 (2.0)	2.9 (1.9)	2.6 (0.6)
Median (minimum, maximum)	3.0 (0.0, 7.1)[c]	2.4 (0.1, 6.9)	2.4 (2.0, 4.9)[d]
Age at PD symptom onset, mean (SD)	58.4 (10.7)	58.8 (9.9)	59.7 (9.9)

[a]$P < 0.05$ versus sPD.
[b]$P < 0.05$ versus *GBA* PD.
[c]Two *GBA* PD subjects had disease durations <7 years at screening, but exceeded 7 years by the time of their baseline assessment.
[d]Seven sPD subjects had disease durations <2 years at screening, but exceeded 4 years at year 2 as a result of scheduling delays; 10 sPD subjects had disease durations >2 years at screening, but a waiver was granted allowing them to enroll in the study.
Report generated on data submitted as of July 1, 2019. *P* values were found using *t* tests (age and age at PD symptom onset), Wilcoxon rank-sum tests (disease duration), and χ^2 tests (all categorical variables).
PD, Parkinson's disease; *GBA*, glucosylceramidase beta; *LRRK2*, leucine rich kinase 2; sPD, sporadic PD; BL, baseline; SD, standard deviation.

TABLE 2. PD characteristics

Variable	*GBA* PD BL Visit, N = 80	*LRRK2* PD BL Visit, N = 158	sPD Year 2 Visit, N = 361	*P* Values *GBA* vs. *LRRK2*	*GBA* vs. sPD	*LRRK2* vs. sPD
MDS-UPDRS total score, *off*				0.1027	0.7649	0.0078
Mean (SD)	42.2 (15.6)	37.3 (19.4)	42.8 (16.8)			
Missing	19	45	92			
MDS-UPDRS part I				0.6767	0.8107	0.7778
Mean (SD)	7.8 (5.2)	8.1 (6.0)	7.7 (5.0)			
Missing	0	2	0			
MDS-UPDRS part II				0.3102	0.6287	0.0400
Mean (SD)	7.9 (5.7)	7.0 (5.8)	8.0 (5.3)			
Missing	0	1	2			
MDS-UPDRS part III, *off*				0.0275	0.5762	0.0002[a]
Mean (SD)	26.2 (10.8)	22.1 (11.6)	27.2 (11.1)			
Missing	19	45	91			
MDS-UPDRS part IV, total score				0.2850	0.0027	0.0166
Mean (SD)	1.9 (2.8)	1.4 (2.6)	0.7 (1.8)			
Missing	7	13	66			
MDS-UPDRS part IV, dyskinesias				0.7402	0.0435	0.0320
Mean (SD)	0.4 (0.9)	0.3 (0.9)	0.1 (0.5)			
Missing	7	13	66			
MDS-UPDRS part IV, motor fluctuations				0.4043	0.0160	0.0509
Mean (SD)	1.2 (1.8)	0.9 (1.7)	0.5 (1.3)			
Missing	7	13	66			
Hoehn & Yahr, *off*				0.8916	0.7463	0.5727
Stages 0–2, n (%)	56 (91.8)	104 (92.0)	259 (95.6)			
Stages 3–5, n (%)	5 (8.2)	9 (8.0)	12 (4.4)			
Missing	19	45	90			
Modified Schwab & England ADL				0.1387	0.4629	0.0025
Mean (SD)	89.3 (10.6)	91.2 (10.7)	88.7 (7.8)			
Missing	0	1	1			
TD/Non-TD classification, *off*				0.2614	0.2282	0.0019
TD, n (%)	35 (57.4)	55 (48.7)	181 (67.0)			
Missing	19	45	91			
TD/PIGD/indeterminate classification, off				—	—	—
TD, n (%)	35 (57.4)	55 (48.7)	181 (67.0)			
PIGD, n (%)	22 (36.1)	49 (43.4)	61 (22.6)			
Indeterminate, n (%)	4 (6.6)	9 (8.0)	28 (10.4)			
Missing	19	45	91			
MoCA total score				0.5918	0.6534	0.1823
Mean (SD)	26.1 (2.9)	25.9 (3.2)	26.2 (3.2)			
Missing	0	2	3			
SCOPA-AUT total score				0.8937	0.3430	0.1572
Mean (SD)	12.8 (7.3)	12.8 (8.3)	11.5 (6.6)			
Missing	3	7	2			
UPSIT raw score				<0.0001[a]	0.0026	0.0021
Mean (SD)	19.4 (8.2)	25.0 (7.8)	22.1 (8.2)			
Missing	4	7	0			
Epworth Sleepiness Scale				0.2600	0.6297	0.3240
Mean (SD)	6.5 (4.2)	7.1 (4.7)	6.7 (4.2)			
Missing	3	4	1			
RBDSQ				<0.0001[a]	0.0799	0.0002[a]
Mean (SD)	5.3 (3.7)	3.5 (2.3)	4.6 (3.0)			
Missing	2	1	0			
Categorical RBDSQ				0.0009[a]	0.0928	0.0112
Positive, >4, n (%)	41 (52.6)	46 (29.3)	151 (41.8)			
Missing	2	1	0			
Total LED				0.8752	0.9176	0.9289
Mean (SD)	333.0 (411.1)	331.0 (330.4)	315.7 (323.0)			

[a]Significance defined at $P < 0.001$.
Report generated on data submitted as of July 1, 2019. *P* values were found using linear or logistic regression models adjusting for gender and disease duration. MDS-UPDRS part IV (dyskinesias) subscore composed of items 4.1 and 4.2. MDS-UPDRS part IV (motor fluctuations) subscore composed of items 4.3 to 4.5. UPSIT results at BL were used for the sPD cohort (because it was not collected at the year 2 visit). Non-TD includes PIGD and indeterminate groups.
PD, Parkinson's disease; *GBA*, glucosylceramidase beta; *LRRK2*, leucine rich kinase 2; sPD, sporadic PD; BL, baseline; SD, standard deviation; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; TD, tremor dominant; PIGD, postural instability/gait difficulty; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scales for Outcomes in PD–Autonomic; UPSIT, University of Pennsylvania Smell Identification Test; LED, levodopa equivalent dose; RBDSQ, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire.

TABLE 3. Cognitive performance

Variable	*GBA* PD BL Visit, N = 80	*LRRK2* PD BL Visit, N = 158	sPD Year 2 Visit, N = 361	*P* Values		
				GBA vs. *LRRK2*	*GBA* vs. sPD	*LRRK2* vs. sPD
Benton JLO score				0.7827	0.0202	0.0007[a]
Mean (SD)	12.0 (2.7)	11.8 (2.9)	12.8 (2.2)			
Missing	3	6	4			
HVLT-R immediate recall				0.9116	0.6996	0.5087
Mean (SD)	24.2 (5.1)	24.3 (5.2)	23.7 (5.4)			
Missing	3	4	0			
HVLT-R delayed recall				0.9324	0.7110	0.5463
Mean (SD)	8.2 (3.0)	8.2 (3.0)	8.2 (2.9)			
Missing	3	4	0			
HVLT-R retention				0.7632	0.3293	0.0894
Mean (SD)	0.83 (0.25)	0.82 (0.23)	0.85 (0.23)			
Missing	3	4	0			
HVLT-R discrimination recognition				0.2919	0.0542	<0.0001[a]
Mean (SD)	10.2 (1.7)	9.8 (2.5)	10.7 (2.4)			
Missing	3	5	0			
Letter number sequencing raw score				0.1070	0.9263	0.0283
Mean (SD)	10.4 (2.9)	9.7 (3.0)	10.3 (2.8)			
Missing	4	5	0			
Semantic fluency total score				0.2589	0.3346	0.7165
Mean (SD)	50.6 (12.1)	48.9 (12.6)	48.6 (12.7)			
Missing	3	5	0			
Symbol digit modalities score				0.3227	0.1261	0.5660
Mean (SD)	37.8 (11.2)	39.6 (11.7)	39.9 (10.9)			
Missing	3	4	0			
Cognitive state, clinician rating				0.7680	0.3139	0.0905
Normal cognition, n (%)	67 (87.0)	136 (88.9)	297 (83.7)			
Mild cognitive impairment/dementia, n (%)	10 (13.0)	17 (11.1)	58 (16.3)			
Missing	3	5	6			
At least 2 scores >1.5 SD below standardized mean				0.7541	0.5893	0.8058
No, n (%)	61 (81.3)	121 (82.9)	304 (84.2)			
Yes, n (%)	14 (18.7)	25 (17.1)	57 (15.8)			
Missing	5	12	0			

[a]Significance defined at $P < 0.0017$.
Report generated on data submitted as of July 1, 2019. *P* values were found using linear or logistic regression models adjusting for gender and disease duration.
GBA, glucosylceramidase beta; PD, Parkinson's disease; *LRRK2*, leucine rich kinase 2; sPD, sporadic PD; BL, baseline; Benton JLO, Benton Judgement of Line Orientation; SD, standard deviation; HVLT-R, Hopkins Verbal Learning Test–Revised.

the groups (Table 3). Comparison of psychiatric and sleep domains revealed higher QUIP (impulse control disorder) scores, but no difference in other psychiatric domains and no difference in RBDSQ scores between the groups (Tables 2 and 4). There was no difference in utilization of the psychotropic medications between the groups (Table 4). Analysis of DAT imaging results revealed higher (better) SBRs in the contralateral caudate and putamen in the GBA PD patients when compared with the sPD patients (Table 5).

LRRK2 PD Versus sPD

A total of 158 *LRRK2* PD patients and 361 sPD patients were included in the analysis. Baseline demographics, PD family history, and type of genetic mutation (for the *LRRK2* PD cohort) are presented in Table 1. There was no difference in age, education, age of onset, or disease duration between the *LRRK2* PD patients and the sPD patients. The *LRRK2* cohort had more than 50% female participants compared with male predominance in the sPD cohort. There were more Hispanics and there was also a higher percentage of first-degree relatives with PD in the *LRRK2* cohort. A majority (89%) of the *LRRK2* PD patients carried the G2019S mutation, consistent with the AJ targeted recruitment strategy. Key PD clinical characteristics of the cohorts are summarized in Table 2. The *LRRK2* PD patients had lower MDS-UPDRS part III *off* motor scores. There was no difference in the part IV score or in LED. There was a trend to higher proportion of nontremor dominant PD phenotype. The evaluation of sleep domains indicated lower RBDSQ scores in the *LRRK2* PD group. Assessment of the cognitive characteristics of the participants revealed no difference in the MoCA score (Table 2), but subtle differences in the detailed neurocognitive battery (Benton Judgement of Line Orientation and Hopkins Verbal Learning Test

TABLE 4. Psychiatric symptoms

Variable	*GBA* PD BL Visit, N = 80	*LRRK2* PD BL Visit, N = 158	sPD Year 2 Visit, N = 361	*P* Values		
				GBA vs. *LRRK2*	*GBA* vs. sPD	*LRRK2* vs. sPD
GDS				0.6959	0.4957	0.1494
Mean (SD)	3.0 (3.0)	3.1 (3.1)	2.7 (2.9)			
Missing	3	5	1			
Categorical GDS				0.1872	0.9184	0.0762
Depressed, >4, n (%)	14 (18.2%)	40 (26.1%)	65 (18.1%)			
Missing	3	5	1			
STAI state subscore				0.5655	0.4298	0.0647
Mean (SD)	33.7 (9.8)	34.6 (10.6)	32.6 (10.0)			
Missing	3	4	0			
STAI trait subscore				0.5934	0.1298	0.0065
Mean (SD)	34.6 (10.0)	35.4 (10.2)	32.6 (9.3)			
Missing	3	5	0			
Any QUIP disorder				0.6184	0.0004[a]	0.0002[a]
Any 1 or more disorders, n (%)	31 (40.3)	54 (35.3)	73 (20.2)			
Missing	3	5	0			
MDS-UPDRS part II, apathy				0.1834	0.0696	0.6373
Normal, n (%)	66 (82.5)	118 (75.6)	264 (73.1)			
Slight, n (%)	10 (12.5)	30 (19.2)	62 (17.2)			
Mild, n (%)	4 (5.0)	5 (3.2)	27 (7.5)			
Moderate, n (%)	0 (0.0)	2 (1.3)	7 (1.9)			
Severe, n (%)	0 (0.0)	1 (0.6)	1 (0.3)			
Missing	0	2	0			
MDS-UPDRS part II, hallucinations and psychosis				0.8826	0.9533	0.9034
Normal, n (%)	73 (91.3)	144 (92.3)	335 (92.8)			
Slight, n (%)	6 (7.5)	10 (6.4)	22 (6.1)			
Mild, n (%)	1 (1.3)	2 (1.3)	3 (0.8)			
Moderate, n (%)	0 (0.0)	0 (0.0)	1 (0.3)			
Severe, n (%)	0 (0.0)	0 (0.0)	0 (0.0)			
Missing	0	2	0			
Antidepressants, yes, n (%)	22 (27.5)	38 (24.1)	90 (24.9)	0.4812	0.6817	0.6381
Antipsychotics, yes, n (%)	1 (1.3)	1 (0.6)	2 (0.6)	0.8387	0.4259	0.3079
Anxiolytics-hypnotics, yes, n (%)	17 (21.3)	38 (24.1)	64 (17.7)	0.6403	0.5524	0.1531

[a]Significance defined at $P < 0.0017$.
Report generated on data submitted as of July 1, 2019. *P* values were found using linear or logistic regression models adjusting for gender and disease duration. For QUIP, the models also adjusted for LED calculated for dopamine agonists class of drugs. For apathy and hallucinations, we are modeling "normal" versus everything else.
GBA, glucosylceramidase beta; PD, Parkinson's disease; *LRRK2*, leucine rich kinase 2; sPD, sporadic PD; BL, baseline; GDS, Geriatric Depression Scale; SD, standard deviation; STAI, State-Trait Anxiety Inventory; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale.

discrimination recognition scores) between the groups (Table 3). A comparison of psychiatric domains revealed higher QUIP (impulse control disorder), but no difference in other psychiatric domains (Table 4). There was no difference in the utilization of the psychotropic medications between the groups (Table 4). Similar to the *GBA* PD patients, an analysis of the DAT imaging results revealed higher (better) SBRs in the contralateral caudate and putamen in the *LRRK2* PD patients when compared with the sPD patients (Table 5).

GBA Versus *LRRK2* PD

There was no difference in age, gender, education, age of onset, or disease duration between the *GBA* and *LRRK2* PD patients. The *LRRK2* cohort had more Hispanics, and there was also a higher percentage of first-degree relatives with PD when compared with the *GBA* cohort (Table 1). The *LRRK2* PD patients had higher (better) University of Pennsylvania Smell Identification Test (hyposmia) scores. A comparison of sleep domains revealed higher RBDSQ scores among the *GBA* PD patients. There was no difference in the MoCA scores or in the detailed neurocognitive battery between the groups (Tables 2 and 3). A comparison of LED, psychiatric, and psychotropic medications indicated no differences between the groups (Tables 2 and 4). There was no difference in DAT imaging results between the groups (Table 5).

Sensitivity Analysis

In addition, to ensure that the study conclusions were not being influenced by participants with outlying disease duration values, sensitivity analyses were conducted on a reduced sample that restricted sPD

TABLE 5. Dopamine transporter 123-I ioflupane single photon emission computed tomography imaging results

Variable	*GBA* PD BL Visit, N = 80	*LRRK2* PD BL Visit, N = 158	sPD Year 2 Visit, N = 361	*P* Values		
				GBA vs. *LRRK2*	*GBA* vs. sPD	*LRRK2* vs. sPD
Contralateral caudate SBR				0.4738	0.0021[a]	0.0020[a]
Mean (SD)	1.74 (0.74)	1.70 (0.52)	1.52 (0.52)			
Minimum, maximum	0.49, 3.90	0.60, 3.35	0.06, 3.52			
Missing	20	27	28			
Ipsilateral caudate SBR				0.3737	0.0288	0.1034
Mean (SD)	1.98 (0.76)	1.92 (0.56)	1.81 (0.58)			
Minimum, maximum	0.36, 4.08	0.54, 3.64	0.25, 3.72			
Missing	20	27	28			
Contralateral putamen SBR				0.2112	<0.0001[a]	<0.0001[a]
Mean (SD)	0.73 (0.45)	0.69 (0.33)	0.56 (0.22)			
Minimum, maximum	0.19, 2.45	0.17, 2.27	0.03, 1.64			
Missing	20	27	28			
Ipsilateral putamen SBR				0.3533	0.0053	0.0168
Mean (SD)	0.86 (0.48)	0.82 (0.32)	0.74 (0.32)			
Minimum, maximum	0.24, 2.79	0.21, 1.90	0.01, 2.12			
Missing	20	27	28			

[a]Significance defined at $P < 0.0042$.
Report generated on data submitted as of July 1, 2019. *P* values were found using linear regression models adjusting for gender and disease duration.
GBA, glucosylceramidase beta; PD, Parkinson's disease; *LRRK2*, leucine rich kinase 2; sPD, sporadic PD; BL, baseline; SBR, specific binding ratio; SD, standard deviation.

disease duration to 2 to 4 years and 0 to 6 years for the *GBA* and *LRRK2* PD patients. That analysis supported all the major conclusions aside from the difference in contralateral caudate SBR between *LRRK2* and sPD lost significance ($P = 0.0065$), although the mean values remained unchanged (Supporting Information Tables S1-5).

Discussion

Here we report the motor and nonmotor phenotype of a large cohort of *LRRK2* and *GBA* mutation carriers with a relatively short disease duration when compared with sPD. Although our data largely confirm the previously published descriptions of the phenotypic characteristics of *LRRK2* PD, it also provides several novel observations regarding *GBA* PD and generates several hypotheses that require additional longitudinal follow-up. Although previous reports demonstrate faster motor and cognitive progression with *GBA* mutations, and slower progression with *LRRK2* mutations, the timeline of the dissociation of the phenotypes from sPD is not well defined, and these data are crucial for clinical trial design. We demonstrate that in the first 3 years, motor and cognitive symptoms are similar in *GBA* PD (N370S) and sPD, highlighting the effect of disease duration on the *GBA* phenotype. In contrast, however, *LRRK2* carriers already start to demonstrate milder motor progression.

GBA PD is reported to be associated with faster rates of motor and cognitive progression as well as a higher prevalence of nonmotor symptoms including cognitive dysfunction, RBD, hyposmia, and autonomic dysfunction when compared with sPD.[4,12,13,27-31] Although these characteristics are more pronounced in "severe" *GBA* mutations (L444P), they are reported in "mild" mutations inclusive of N370S.[27,32] Our analysis did not reveal significant differences between *GBA* and sPDs in any of these domains. Our results do not contradict the previously published data as most reports indicate a difference in the rate of progression and not baseline findings.[27] Our current analysis is restricted to cross-sectional data and includes mostly N370S mild *GBA* PD participants relatively early in the disease course. Longitudinal follow-up will reveal the difference in the slopes of progression between the 2 groups. However, a lack of significant nonmotor symptom burden at the early stage of the disease opens a window of opportunity for the disease-modifying interventions. Traditionally, disease-modifying interventions are tested in a PD de novo population for the rationale of a lack of confounding effect of dopaminergic therapy and a hope that intervention at the earlier stage of the PD degenerative process will have better chance of success. However, the recruitment of genetic PD de novo cohorts will be challenging, and our data provide additional justification to include early symptomatically treated *GBA* PD participants into disease-modifying interventional studies. Consideration may be given to using time to onset of cognitive impairment and other nonmotor milestones as the primary outcomes, especially considering more rapid progression of these symptoms in *GBA* PD including the mild N370S form.[27] The strengths of our data include a deep phenotypic characterization that will allow in-depth future longitudinal analysis that will enable such studies.

There also is tremendous interest to test disease-modifying interventions in the premotor phases of PD. *GBA* premotor cohorts have been reported to have a higher rate of RBD and cognitive impairment.[6,33] Interestingly, we did not identify a higher prevalence of RBD in our *GBA* PD cohort. Again, longitudinal analysis will be essential to track the timeline of the progression of these features. It should be noted that our cohort largely includes participants with the N370S *GBA* mutation, known to be associated with a milder PD phenotype, and should be interpreted as such.

Contrary to the *GBA* PD, *LRRK2* PD specifically G2019S mutation carriers are reported to have less motor and nonmotor disabilities, less hyposmia, RBD, and a slower rate of PD progression when compared with sPD.[34-36] Our data are largely consistent with the previous reports from other studies including *LRRK2* consortium analysis.[34-36] Consistent with the previous reports, our largely G2019S *LRRK2* PD cohort had less motor disability and lower RBDSQ scores when compared with the sPD cohort. We identified a trend to a higher percentage of nontremor dominant phenotype in our cohort as was previously reported.[34] Although there was no meaningful difference in cognitive performance between the *LRRK2* and sPD cohorts, we did not identify better cognitive performance in the *LRRK2* PD patients as was previously reported.[36] The latter could be attributed to an earlier stage of PD in both cohorts and a lack of significant cognitive impairment in sPD. Indeed, differentiators of our cohort compared with the previously published datasets are younger age at recruitment and shorter disease durations. The latter will be important for the longitudinal analysis as currently available data included participants with the mean disease duration at recruitment of 8.2 (6.0) years and modeled the slope of progression in the early phase.[18] Our cohort, although not de novo at recruitment, has a mean disease duration 2.9 (1.9) years at baseline, which will allow collecting actual progression data and validating previously reported results.

Interestingly, both genetic cohorts had higher scores on impulse control disorders scale when compared with the sPD cohort, with no difference in total LED and specifically dopamine agonists therapy. These findings have not been previously reported in *LRRK* or *GBA*, but have been reported in parkin PD.[37] The underlying biology remains to be determined. Although significant, the QUIP scores were low, and longitudinal data will be essential to determine whether this is a true differential feature of both genetic cohorts. There was no difference in the other psychiatric domains in either cohort.

Consistent with the previous reports, the *LRRK2* and *GBA* PD cohorts had a higher percentage of female participants when compared with the male gender predominance seen in the sPD cohorts.[38,39] The biology of male gender predominance in PD has not been well established, but the lack of such might point to the genetic effect being upstream of the gender.

One interesting and novel observation in this study is the relatively higher (better) SBR DAT binding in both genetic cohorts when compared with the sPD cohort. The difference was restricted to the side contralateral to the body side more affected by the PD symptoms. The biology of this observation is to be elucidated but raises a hypothesis of slower rate of decline in DAT in genetic PD compared with sPD. Alternatively, this finding could be a result of disruption of dopamine release prior to loss of dopaminergic terminals. Reduced synaptic dopamine might lead to reduced occupancy of the dopamine transporter, thereby contributing to a false estimation of DAT binding. Abnormal dopamine release has been demonstrated in *GBA* models.[40] Other groups have reported no difference in DAT or positron emission tomography binding between the sPD and *LRRK2* cohorts, although the sample size was small.[41-43] A more pronounced DAT deficit has been reported in *GBA* PD, but that was driven by severe (L444P) mutation and not observed in N370s participants.[27] Interestingly, we have demonstrated increased SBR DAT binding in all striatal regions in *GBA* but not *LRRK2* nonmanifest mutation carriers compared with healthy controls.[44] Longitudinal follow-up of both at-risk and PD-manifest genetic cohorts will be essential to further elucidate the progression of DAT deficit in these cohorts.

Another strength of the data is parallel ascertainment of *GBA* and *LRRK2* PD cohorts with the same scope of activities. The baseline comparison reflects known phenotypic characteristics of each cohort as summarized previously, but the data provide a foundation for future longitudinal analysis to compare the slope and scope of progression of the participants followed in the same study.

Limitations

We recognize that this analysis has several limitations. First, *LRRK2* and *GBA* PD genetic testing was restricted to a panel of limited gene variants most commonly present in the AJ population. Both *LRRK2* (predominantly G2019S) and *GBA* (predominantly N370S) represent selected mutations of both genes increasing our power to understand the effect of those mutations but limiting conclusions on *LRKK2* or *GBA* mutations in general. Both of these mutations are known to be associated with a milder phenotype. Although we had a small proportion (less than 10%) of carriers of more severe mutations in both cohorts (L444P *GBA* and R1441G *LRRK2*), the number was too small to run a comparative analysis. Larger cohorts with broader ascertainment of pathogenic mutations in both genes will be necessary to analyze the effect of specific mutation on phenotypic manifestations and rate of progression.

A higher percentage of *LRRK2* and *GBA* PD patients did not have DAT SPECT results (17% and 25%, respectively) versus 8% in the sPD patients, which could impact the analysis and conclusions. Because of the challenges in the recruitment of genetic PDs, they were allowed to participate in the study even if they declined DAT SPECT. Despite some missing data, to our knowledge this is still the largest reported PD genetic cohort with DAT imaging. The PPMI study places significant emphasis on retention and data completeness, and all attempts will be made to obtain longitudinal DAT imaging data.

This analysis does not include spinal fluid or blood-based biomarkers data as these were not available at the time of this article and will be reported in future publications.

Genetic PD cohorts were recruited with disease duration up to 7 years. Although there was no difference in the mean disease duration between the cohorts, the range was wider in the genetic PD cohort, which could have impacted the analysis. However, our sensitivity analysis on a subset of participants with a shorter disease duration supported our major conclusions.

Finally, we recognize that we report baseline characteristics and that longitudinal follow-up is crucial to confirming these observations and comparing slope and scope of progression in genetic versus sPD cohorts. The PPMI study is committed to the comprehensive longitudinal follow-up of these participants and reporting these data as they become available.

In conclusion, we report baseline clinical and DAT imaging characteristics of *GBA* and *LRRK2* PD cohorts. Early in the course of the disease, the *GBA* cohort was largely phenotypically indistinguishable from the sPD cohort, whereas the *LRRK2* PD cohort had less motor and nonmotor disability. Interestingly, both genetic cohorts demonstrated less DAT transporter loss when compared with the sPD cohort, suggesting that there might be a difference in the slope of progression of dopaminergic terminal loss. Longitudinal data on the evolution of the clinical, DAT imaging, and biological characteristics of both genetic cohorts will be essential to define the slope of progression.

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APPENDIX

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Supporting Data

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