ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Clinical features and progression of Parkinson's disease with LRRK2 variants: A prospective study

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Received: 28 July 2024; Revised: 15 October 2024; Accepted: 21 October 2024

Annals of Clinical and Translational Neurology **2025; 12(1): 34–42**

doi: 10.1002/acn3.52244

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Abstract

Objective: We established a prospective cohort study to investigate the differences in motor and non-motor symptoms between idiopathic Parkinson's disease (IPD) and Parkinson's disease in carriers of leucine-rich repeat kinase 2 (LRRK2) gene risk variants (LRRK2-PD). **Methods**: The study included 1407 individuals with IPD and 649 individuals with LRRK2-PD (comprising 304 with LRRK2-G2385R, 220 with LRRK2-R1628P, and 105 with LRRK2-A419V). Differences in symptoms between LRRK2-PD and IPD were analyzed using LCMM modeling and Cox regression analysis. **Results**: The LRRK2-G2385R variant showed slower progression in tremor symptoms and excessive daytime sleepiness compared with IPD. In contrast, symptoms associated with LRRK2-R1628P and LRRK2-A419V were more similar to those of IPD. Survival analysis revealed that LRRK2-PD does not affect life expectancy compared with IPD. **Interpretation**: Our extended longitudinal follow-up of LRRK2-PD in the Chinese population provided valuable insights, further confirming the clinical characteristics of the three LRRK2 variants.

Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, characterized by typical motor manifestations and diverse non-motor symptoms.[1] Although the exact pathogenesis of PD remains unclear, it is believed to involve a combination of genetic factors, environmental risks, and aging.[2] Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene account for 2–4.5% of autosomal dominant PD cases and 0.32–1.7% of sporadic early-onset PD in the Chinese population.[3–5] Besides pathogenic mutations, several risk variants in LRRK2 have been identified, including A419V, R1628P, and G2385R, which are prevalent in the Chinese population but rare in the White population.[6–8] The frequency of LRRK2 variants varies significantly across different populations. The LRRK2-G2019S variant is most common, especially among North African Arabs and Ashkenazi Jews, followed by North American and Southern European populations, but is rare in the Chinese population.[9–12]

The clinical presentation of LRRK2-related PD (LRRK2-PD) generally aligns with idiopathic PD (IPD).[13,14] However, disease progression, motor symptoms, and non-motor symptoms in LRRK2-PD have shown variability compared with IPD.[9,15] For instance, the age of onset for PD patients carrying the LRRK2-G2019S mutation among Ashkenazi Jews was not significantly different from those with IPD.[16] Contrastingly, another study on Ashkenazi Jews indicated a younger age at onset for PD patients with the LRRK2-G2019S mutation, although this mutation did not affect the rate of motor disease progression.[17] A multicenter study of PD patients with the two most common variants, LRRK2-G2019S and LRRK2-G2385R, found that G2385R carriers experienced faster motor symptom progression and a higher frequency of motor fluctuations, while G2019S carriers had slower motor symptom progression.[6] However, in Asian populations, motor symptoms in LRRK2-G2385R carriers did not differ significantly from those in IPD, and LRRK2-G2385R was associated with a more benign course regarding certain autonomic symptoms and cognitive deficits.[18–20] Although the phenotypes of LRRK2-G2019S and LRRK2-G2385R are well-studied, comprehensive clinical investigations of LRRK2-PD with the A419V and R1628P variants, especially A419V, remain scarce. Additionally, survival analyses have shown that patients with LRRK2-G2019S may have longer survival compared with those with IPD,[21] and that those with LRRK2 mutations may experience lower mortality.[22]

Given the genetic heterogeneity of LRRK2 across different ethnic groups, we established a prospective cohort study to evaluate the clinical features of LRRK2-PD. This study aimed to characterize the specific clinical features of the LRRK2 variants G2385R, R1628P, and A419V by comparing the motor and non-motor symptoms between patients with IPD and those with LRRK2-PD variants.

Methods

Study design and participants

We conducted a prospective cohort study to investigate differences in motor and non-motor symptoms between IPD and LRRK2-PD (clinical trial: NCT03523104). Participants were recruited between February 2017 and December 2020 at Xiangya Hospital, Central South University, and other sites within the Parkinson's Disease and Movement Disorders Multicenter Database and Collaborative Network in China (http://pd-mdcnc.com). All patients were diagnosed with PD by experienced neurologists using the United Kingdom Brain Bank Clinical Diagnostic Criteria for PD[23] or the 2015 International Parkinson's and Movement Disorder Society Clinical Diagnostic Criteria for PD.[24] Additionally, using whole-genome and whole-exome sequencing (WGS/WES) combined with multiplex ligation-dependent probe amplification and rare deleterious variant analysis (including copy number variation, single-nucleotide variation, and insertions/deletions), we excluded pathogenic mutations in known PD-causing genes and the GBA gene. LRRK2-PD patients included in the WGS/WES analysis had LRRK2 variants such as G2385R, R1628P, or A419V, while IPD patients excluded those with the aforementioned variants.[5,8] Eventually, the study included 1407 cases of IPD and 649 cases of LRRK2-PD, among LRRK2-PD cases, there were 304 cases with the LRRK2-G2385R mutation, 220 cases with the LRRK2-R1628P mutation, 105 cases with the LRRK2-A419V mutation, and 20 cases carrying at least two LRRK2 mutations. The cutoff follow-up date for all patients was December 2023, with a face-to-face follow-up duration averaging 5.59 ($\pm$1.27) years. Participants had at least one study visit and follow-ups were conducted in person. The study was approved by the ethics committee and written informed consent was obtained from each participant and from collaborating centers, including the Second Xiangya Hospital of Central South University, Third Xiangya Hospital of Central South University, and First Affiliated Hospital of the University of South China.

Clinical and neuropsychological assessment measures

Participants underwent comprehensive and standardized clinical assessments. All researchers were trained to ensure a consistent understanding of the scales, methods, and phrasing used for clinical data collection. Baseline clinical information, including age, sex, age at onset, and disease duration, was collected. Motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr stages. UPDRS-III scores were subdivided into tremor, rigidity, and bradykinesia scores.

Non-motor symptoms were assessed using the Mini-Mental State Examination (MMSE), Rapid Eye Movement Sleep Behavior Disorder Questionnaire-Hong Kong (RBDQ-HK), Epworth Sleepiness Scale (ESS), Hyposmia Rating Scale (HRS), and Functional Constipation Diagnostic Criteria Rome III. Cognitive impairment was identified based on MMSE scores, with thresholds adjusted for literacy levels (17, 20, and 24, respectively). Probable rapid eye movement sleep behavior disorder was defined as an RBDQ-HK score of at least 18. Excessive daytime sleepiness (EDS) was defined as an ESS score >10. Hyposmia was defined as an HRS score <22.5. Details regarding these clinical scales have been provided in previous studies.[25–28]

Statistical analysis

Descriptive statistics are presented as mean ± standard deviation for continuous variables and percentage frequency for categorical variables. Between-group comparisons of demographic characteristics were performed using Student's *t*-test, Mann–Whitney *U*-tests, and chi-square tests. Differences in clinical characteristics at baseline were compared using multiple linear regression for continuous variables and logistic regression for categorical variables, with adjustments for sex, age at onset, and disease duration. We applied the Bonferroni correction for the multiple comparisons reported here.

Latent-class mixed models were established using R software (version 4.3.2, lcmm package) to examine the association between LRRK2 mutations and the rate of change in motor symptom scores, using PD duration (from age at onset) as the time scale. The primary model included the LRRK2 mutant genotype as the main independent variable, adjusted for sex, baseline age, and PD duration as fixed effects, with participant-specific random effects to account for repeated measures within the same participant. For Hoehn and Yahr stage (>2.5), EDS, rapid eye movement sleep behavior disorder, and cognitive impairment, the effect of different LRRK2 mutations on the occurrence of these categorical variables was investigated using the Cox proportional hazards model, with PD duration (from age at onset) as the time scale and age at onset and sex as fixed variables in the model.

The Kaplan–Meier method was used to graphically describe the evolution of patient-specific symptoms and plot survival curves for IPD and LRRK2-PD, with comparisons made using the log-rank test. Two-tailed *p*-values <0.05 were considered statistically significant.

Results

Demographic characteristics

Figure S1 details the participant recruitment and selection process. Table 1 demonstrates the differences in baseline characteristics between LRRK2-PD and IPD, showing no significant differences in age at onset, disease duration, BMI, proportion of late-onset PD, or education. However, the proportion of males was lower in patients with LRRK2-PD (46.2%) compared with IPD (52.6%), particularly among the LRRK2-G2385R (43.8%) and LRRK2-A419V (44.8%) variants (Table 1).

Baseline characteristics and evolution of motor symptoms at follow-up

We compared baseline motor symptoms between the groups and found that the tremor scores in the UPDRS differed between LRRK2-PD (3.71 ± 3.57) and IPD (3.27 ± 3.31), with tremor scores being lower in the LRRK2-PD group, particularly in the LRRK2-G2385R variant (3.18 ± 3.05). However, no differences were

Table 1. Characteristics of baseline.

Variable	IPD (*n* = 1407)	LRRK2-PD				*p*-value IPD versus LRRK2-PD
		LRRK2-PD (*n* = 649)	LRRK2-G2385R (*n* = 304)	LRRK2-R1628P (*n* = 220)	LRRK2-A419V (*n* = 105)	
Gender ratio, male (%)	740 (52.6%)	300 (46.2%)	133 (43.8%)	115 (52.3%)	47 (44.8%)	**0.023**
Age at onset (years)	55.41 ± 10.64	55.05 ± 10.22	55.23 ± 10.2	54.97 ± 10.34	55.81 ± 9.21	0.875
Course of disease (years)	5.88 ± 4.46	5.82 ± 4.64	5.83 ± 4.71	5.92 ± 4.62	5.64 ± 4.26	0.868
Late-onset PD ratio (%)	939 (66.7%)	423 (65.2%)	199 (65.5%)	141 (64.1%)	74 (70.5%)	0.234
Body mass index	22.72 ± 3.56	22.61 ± 3.21	22.68 ± 3.17	22.52 ± 3.35	22.71 ± 3.09	0.519
Education level						0.847
0 year (%)	11 (0.8%)	7 (1.1%)	3 (1.0%)	3 (1.4%)	1 (0.9%)	
1–6 years (%)	449 (31.9%)	182 (28.0%)	84 (27.6%)	59 (26.8%)	31 (29.5%)	
7–12 years (%)	764 (54.3%)	374 (57.6%)	176 (57.9%)	130 (59.1%)	60 (55.5%)	
>12 years (%)	183 (13.0%)	86 (13.3%)	41 (13.5%)	28 (12.7%)	13 (12.4%)	

Categorical variables are reported as numbers and percentages; continuous variables are reported as means ± standard deviations. *p* values were assessed by Mann–Whitney *U*-tests and chi-square tests among the groups. The bold emphasis in the table means $p < 0.05$.

IPD, idiopathic Parkinson's disease; LRRK2-PD, Parkinson's disease with mutations in the LRRK2 gene; LRRK2-A419V, Parkinson's disease of the LRRK2 A419V mutation type; LRRK2-G2385R, Parkinson's disease of the LRRK2 G2385R mutation type; LRRK2-R1628P, Parkinson's disease of the LRRK2 R1628P mutation type.

Table 2. Comparison of the motor symptoms and non-motor symptoms between IPD and LRRK2-PD at baseline.

		LRRK2-PD				*p*-value			
Variable	IPD (n = 1407)	LRRK2-PD (n = 649)	LRRK2-G2385R (n = 304)	LRRK2-R1628P (n = 220)	LRRK2-A419V (n = 105)	P0	P1	P2	P3
UPDRS.I	2.48 ± 2.00	2.41 ± 2.05	2.39 ± 2.07	2.41 ± 1.95	2.48 ± 2.27	0.354	0.349	0.655	0.909
UPDRS.II	11.99 ± 6.31	11.90 ± 6.53	11.9 ± 6.62	12.22 ± 6.41	11.33 ± 6.7	0.71	0.906	0.499	0.332
UPDRS.III	27.51 ± 14.73	26.31 ± 14.51	26.06 ± 14.15	26.59 ± 14.61	26.08 ± 14.72	0.054	0.16	0.382	0.424
Tremor	3.71 ± 3.57	3.27 ± 3.31	3.18 ± 3.05	3.5 ± 3.86	3.01 ± 2.76	**0.011**	**0.022**	0.382	0.055
Rigidity	5.63 ± 4.15	5.44 ± 4.19	5.27 ± 3.97	5.46 ± 4.21	5.68 ± 4.36	0.259	0.318	0.578	0.675
Bradykinesias	10.13 ± 6.38	9.58 ± 6.03	9.44 ± 5.89	9.64 ± 5.94	9.76 ± 6.26	0.138	0.101	0.273	0.655
Hoehn and Yahr stage						0.558	0.485	0.556	0.706
1–2.5	1017 (72.3%)	461 (71.0%)	213 (70.1%)	155 (70.5%)	77 (73.3%)				
3–5	390 (27.7%)	188 (29.0%)	91 (29.9%)	65 (29.5%)	28 (26.7%)				
CDs (%)	141 (10.0%)	64 (9.9%)	27 (8.9%)	22 (10.0%)	12 (11.4%)	0.91	0.411	0.919	0.755
RBD (%)	601 (42.7%)	267 (41.1%)	128 (42.1%)	83 (37.7%)	46 (43.8%)	0.502	0.975	0.164	0.769
EDS (%)	515 (36.6%)	193 (29.7%)	87 (28.6%)	62 (28.2%)	39 (37.1%)	**0.006**	**0.019**	**0.014**	0.773
Hyposmia (%)	597 (42.4%)	259 (39.9%)	114 (37.5%)	88 (40.0%)	50 (47.6%)	0.281	0.191	0.534	0.236
Constipation (%)	676 (48.0%)	279 (43.0%)	130 (42.8%)	94 (42.7%)	47 (44.8%)	0.059	0.133	0.141	0.566

Categorical variables are reported as numbers and percentages; continuous variables are reported as means ± standard deviations. Multiple comparisons were corrected using the Bonferroni method. *p*-value are the results of multifactorial analysis (multiple linear regression for continuous variables, logistic regression for categorical variables, and all clinical variables were adjusted for gender, age at onset, and duration of disease). The bold emphasis in the table means $p < 0.05$. P0 indicates the *p* value of the IPD group compared with the LRRK2-PD group; P1 indicates the *p* value of the IPD group compared with the LRRK2-G2385R group; P2 indicates the *p* value of the IPD group compared with the LRRK2-R1628P group; and P3 indicates the *p* value of the IPD group compared with the LRRK2-A419V group.

IPD, idiopathic Parkinson's disease; LRRK2-PD,Parkinson's disease with mutations in the LRRK2 gene; LRRK2-A419V, Parkinson's disease of the LRRK2 A419V mutation type; LRRK2-G2385R, Parkinson's disease of the LRRK2 G2385R mutation type; LRRK2-R1628P, Parkinson's disease of the LRRK2 R1628P mutation type; UPDRS, Unified Parkinson's Disease Rating Scale; EDS, excessive daytime sleepiness; RBD, rapid eye movement sleep behavior disorder; CDs, cognitive dysfunction.

observed between LRRK2-PD and IPD in the rigidity and bradykinesia scores of the UPDRS or in Hoehn and Yahr staging at baseline (Table 2).

Follow-up data indicated that significant differences in tremor scores according to disease progression persisted between LRRK2-PD and IPD patients (Fig. S2, Table 3). Tremor progression was slower in LRRK2-PD compared with IPD (estimate [SE], −0.153 [0.064] points/year; $p = 0.016$), especially in the LRRK2-G2385R variant (estimate [SE], −0.176 [0.084] points/year; $p = 0.037$). No significant differences in tremor progression were found between IPD and LRRK2-R1628P (estimate [SE], −0.099 [0.095] points/year; $p = 0.298$) or LRRK2-A419V (estimate [SE], −0.196 [0.132] points/year; $p = 0.136$). Other motor symptoms, including Hoehn and Yahr staging, did not differ between LRRK2-PD and IPD (Table 3).

Baseline characteristics and evolution of non-motor symptoms at follow-up

Baseline data showed that the proportion of EDS was lower in the LRRK2-PD group (29.7%) than in the IPD group (36.6%), mainly due to the LRRK2-G2385R (28.6%) and LRRK2-R1628P (28.2%) variants. The proportion of EDS in LRRK2-A419V (37.1%) was not significantly different from IPD. No differences were observed in REM sleep behavior disorder (RBD), cognitive dysfunction, hyposmia, or constipation at baseline between LRRK2-PD and IPD (Table 2).

Follow-up data indicated that differences in non-motor symptoms, particularly EDS, persisted between LRRK2-PD and IPD. The LRRK2-G2385R variant (HR 0.62, 95% CI 0.42–0.93, $p = 0.021$) was found to be a protective factor against EDS, while the difference for the LRRK2-R1628P variant (HR 0.70, 95% CI 0.46–1.06, $p = 0.091$) was not statistically significant (Fig. 2). Kaplan–Meier curves showed that EDS symptoms were delayed in LRRK2-PD patients, with a median disease duration of 18 years compared with 14 years in IPD patients (Fig. 1). There was no significant difference in RBD between LRRK2-PD (HR 0.77, 95% CI 0.58–1.04, $p = 0.084$) and IPD, particularly for LRRK2-G2385R (HR 0.69, 95% CI 0.45–1.05, $p = 0.085$) (Fig. 2). No differences were found in other non-motor symptoms between the LRRK2-PD and IPD groups.

Table 3. Models comparing rate of change in UPDRS among PD (idiopathic PD, LRRK2 PD(LRRK2-G2385R, LRRK2-R1628P and LRRK2-A419V)).

	LRRK2 versus IPD		LRRK2-G2385R versus IPD		LRRK2-R1628P versus IPD		LRRK2-A419V versus IPD	
Characteristic	*B* (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value	*B* (SE)	*p* value
UPDRS-I	−0.037 (0.057)	0.512	−0.076 (0.074)	0.307	0.006 (0.080)	0.937	−0.018 (0.116)	0.879
UPDRS-II	−0.041 (0.066)	0.534	−0.081 (0.088)	0.357	0.038 (0.100)	0.703	−0.094 (0.138)	0.499
UPDRS-III	−0.052 (0.063)	0.412	−0.057 (0.084)	0.499	−0.006 (0.108)	0.957	−0.120 (0.132)	0.363
Tremor	−0.153 (0.064)	**0.016**	−0.176 (0.084)	**0.037**	−0.099 (0.095)	0.298	−0.196 (0.132)	0.136
Rigidity	−0.010 (0.051)	0.851	−0.013 (0.070)	0.855	−0.001 (0.056)	0.979	−0.021 (0.110)	0.849
Bradykinesia	−0.012 (0.060)	0.842	−0.038 (0.079)	0.652	0.053 (0.089)	0.554	−0.065 (0.123)	0.596

In these models, we corrected for age at onset and gender, the various LRRK2 mutants were the independent variables, and the UPDRS component scores were the dependent variables; age at onset, gender, and disease duration were covariates. Regression coefficients (*B*) and adjusted p values were assessed by generalized linear mixed models (LCMM). Bold in the table indicates $p < 0.05$.

IPD, idiopathic Parkinson's disease; LRRK2-PD, Parkinson's disease with mutations in the LRRK2 gene; LRRK2-A419V, Parkinson's disease of the LRRK2 A419V mutation type; LRRK2-G2385R, Parkinson's disease of the LRRK2 G2385R mutation type; LRRK2-R1628P, Parkinson's disease of the LRRK2 R1628P mutation type; UPDRS, Unified Parkinson's Disease Rating Scale.

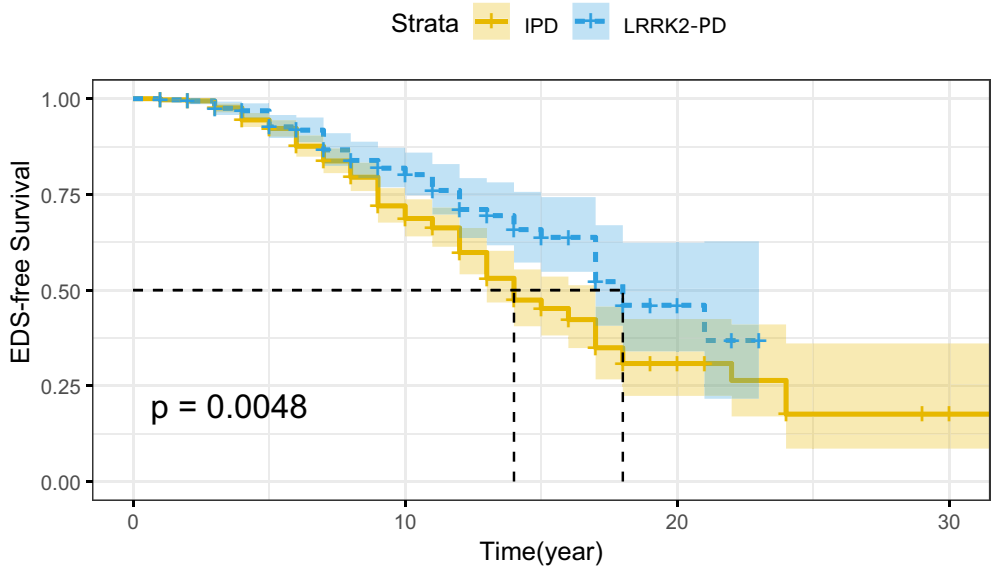

Figure 1. Kaplan–Meier survival chart showing delayed EDS in IPD versus LRRK2-PD. EDS, excessive daytime sleepiness; LRRK2-PD: Parkinson's disease with mutations in the LRRK2 gene; IPD: idiopathic Parkinson's disease.

Mortality and survival time in LRRK2-PD and IPD

A total of 85 LRRK2-PD and 200 IPD patients died, with mortality rates of 13.1% and 14.2%, respectively. The mean ages at death for LRRK2-PD and IPD were 71.61 and 72.06 years, respectively. After adjusting for disease duration and plotting Kaplan–Meier curves, we found no significant difference in survival between LRRK2-PD and IPD ($p = 0.56$), with median survival times of 28.70 and 27.19 years, respectively (Fig. 3).

Discussion

Clinical characterizations of PD with LRRK2 risk variants have predominantly focused on individuals carrying the G2019S mutation, primarily identified in populations of European ancestry, followed by those with the G2385R and R1628P mutations. Our study systematically and prospectively builds on prior longitudinal studies of PD associated with LRRK2 risk variants, including A419V, R1628P, and G2385R. Patients were followed for an average of 5.59 (±1.27) years.

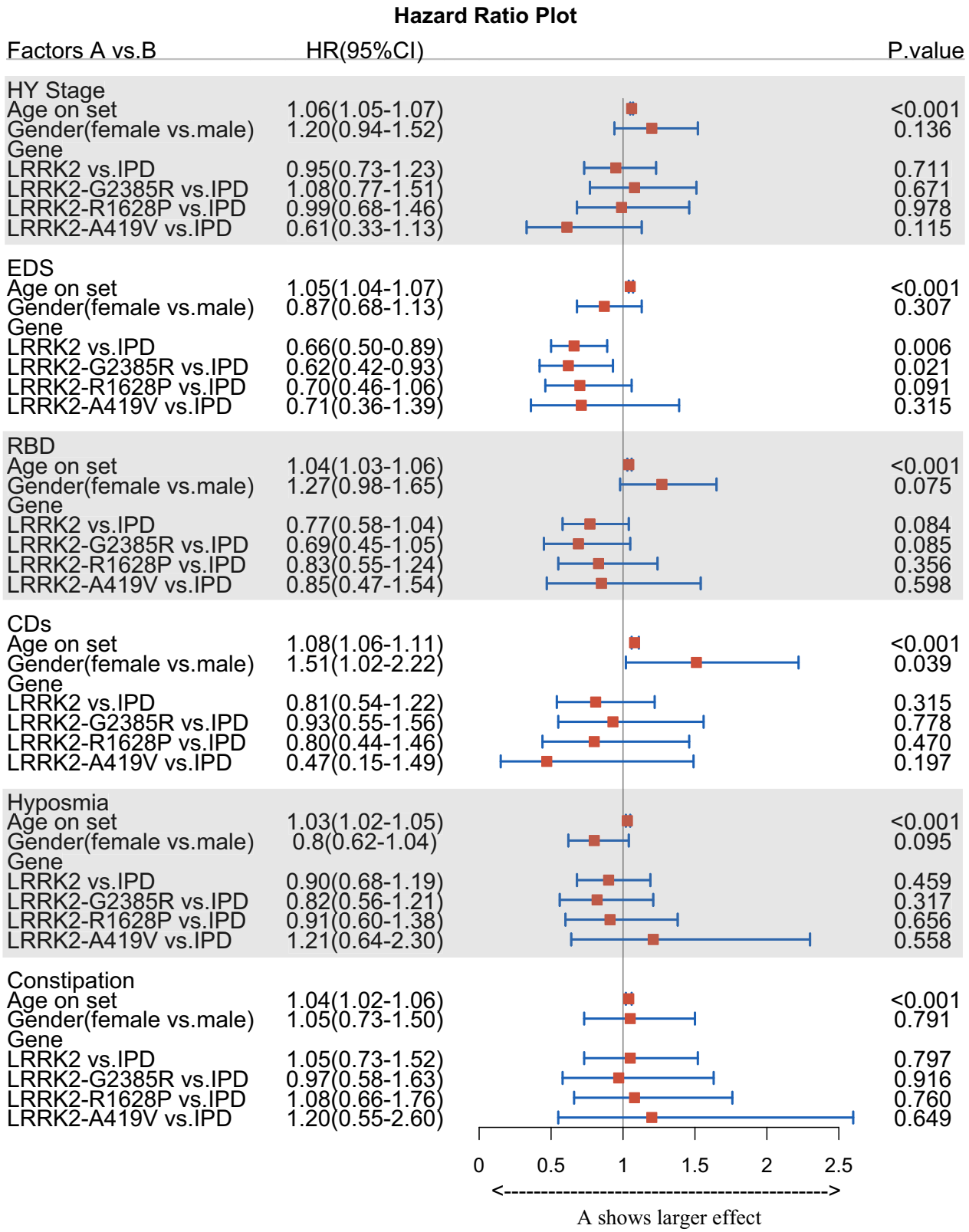

Figure 2. Cox regression analysis of risk factors for HY stage (HY >2.5), EDS, RBD, CDs, hyposmia, and constipation. CDs, cognitive dysfunction; EDS, excessive daytime sleepiness; HY stage, Hoehn and Yahr stage; PD, Parkinson's disease; RBD, rapid eye movement sleep behavior disorder.

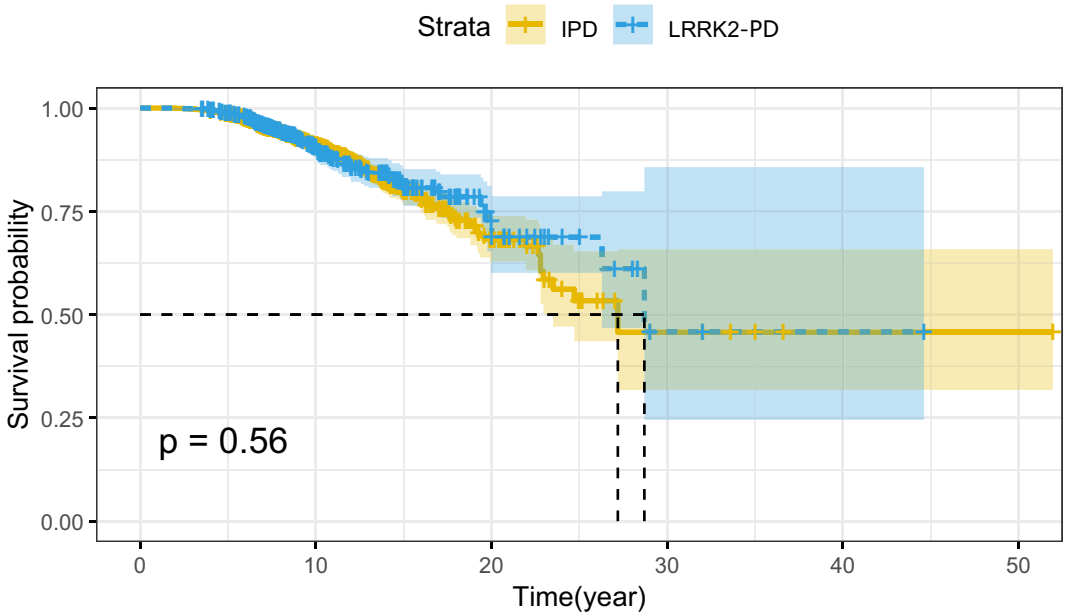

Figure 3. Kaplan–Meier survival chart showing survival probability in IPD versus LRRK2-PD. LRRK2-PD, Parkinson's disease with mutations in the LRRK2 gene; IPD, idiopathic Parkinson's disease.

Previous cross-sectional and follow-up studies on LRRK2-PD with the G2019S variant have shown that motor symptoms are more varied and progress more slowly than in IPD.[6,29,30] However, a comparison of individuals with PD carrying LRRK2 risk variants, without distinguishing between subgroups, suggests that these variants may lead to a faster progression of motor symptoms.[15] Although there was no significant difference in the total UPDRS-III score between the LRRK2-PD and IPD groups at baseline ($p = 0.054$), our results indicated that tremors were relatively uncommon in the LRRK2-PD group compared with the IPD group ($p = 0.011$). We explored whether this difference in tremors could be attributed to a specific LRRK2 risk variant. Our findings revealed that tremors in individuals with the G2385R variant were significantly milder than those in individuals with IPD, suggesting that the difference between LRRK2-PD and IPD may be due to the G2385R variant. Additionally, over the 5.59 ($\pm$1.27) year follow-up, using LCMM modeling to evaluate motor symptoms in the disease progression model, our prospective analysis continued to support the baseline finding that tremor progression in LRRK2-PD with G2385R appears more benign than in IPD.

We assessed daytime sleepiness and observed that its frequency was lower and its onset was delayed in patients with LRRK2 G2385R PD. However, we did not find significant differences between the three LRRK2-PD subtypes and IPD in cognitive function, olfaction, RBD, or constipation, which somewhat contradicts previous studies.[6,30,31]

Given the rarity of survival data among LRRK2-PD patients, especially in our population, we calculated survival curves and assessed whether genetic status influenced mortality compared with IPD. After a follow-up of 5.59 ($\pm$1.27) years, the mortality rate in the LRRK2-PD group was 13.1%, compared with 14.2% in the IPD group. Using the age at onset as the starting point, the median survival was 28.70 years for LRRK2-PD patients and 27.19 years for IPD patients. There was no significant difference in mortality rates and median survival between the LRRK2-PD and IPD groups, indicating that carrying these LRRK2 risk variants did not accelerate the mortality process in PD.

Our study had some limitations. Firstly, our 5-year longitudinal cohort study of patients with LRRK2-PD experienced a decline in retention rates over time. A longer follow-up period is crucial to confirm these observations. Additionally, we evaluated RBD and olfactory function using assessment scales rather than polysomnography or olfactory sniffing tests.

The prospective longitudinal follow-up of patients with the G2385R variant revealed distinct clinical features, whereas the A419V and R1628P variants exhibited symptoms very similar to those of IPD. To our knowledge, this is the first study to report the clinical profiles of patients with the LRRK2-A419V mutation. Furthermore, we conducted the first survival analysis of LRRK2-PD in a Chinese population, comparing it with that of IPD patients.

Studies of LRRK2-PD subtypes and IPD may provide new insights into the pathophysiology and treatment of PD.

Conclusions

Our prospective analysis of a large cohort of patients with three specific LRRK2 mutations in PD revealed that individuals with the LRRK2-G2385R mutation exhibited slower progression in terms of tremor and EDS compared with those with IPD. In contrast, the clinical symptoms of individuals with the LRRK2-A419V mutation were more similar to those observed in IPD. Furthermore, the survival rates of individuals with LRRK2-PD were comparable to those with IPD. These findings underscore the necessity for longitudinal studies of longer duration to further elucidate these observations.

Acknowledgments

We are grateful for the decision of every single participant to take part in this study and we thank all the principal investigators and their team members for enrolling participants. We also acknowledge all our team members in recent years for enrolling participants.

Funding Information

This study was funded by the National Natural Science Foundation of China (No. 82071437), the Hunan Innovative Province Construction Project (Grant No. 2021SK1010, 2023JJ10098, 2023SK2037, and 2019SK2335), and the National Key Research and Development Program of China (No. 2021YFC2501200).

Author Contributions

All authors contributed to the conception and design of this study. The material preparation, data collection, and analyses were performed by Tingwei Song and Xiaoxia Zhou. The first draft of the manuscript was written by Tingwei Song and Qian Xu, and all authors revised the manuscript. All the authors have read and approved the final version of the manuscript.

Conflict of Interest

The authors have no financial disclosures to make.

Data Availability Statement

All data that support the findings of this study are available upon reasonable request to the corresponding author.

References

1. Bloem BR, Okun MS, Klein C. Parkinson's disease. Lancet. 2021;397(10291):2284-2303.
2. Periñán MT, Brolin K, Bandres-Ciga S, et al. Effect modification between genes and environment and Parkinson's disease risk. Ann Neurol. 2022;92(5):715-724.
3. Chen Y-P, Yu S-H, Zhang G-H, et al. The mutation spectrum of Parkinson-disease-related genes in early-onset Parkinson's disease in ethnic Chinese. Eur J Neurol. 2022;29(11):3218-3228.
4. Sun Y-M, Zhou X-Y, Liang X-N, et al. The genetic spectrum of a cohort of patients clinically diagnosed as Parkinson's disease in mainland China. NPJ Parkinsons Dis. 2023;9(1):76.
5. Zhao Y, Qin L, Pan H, et al. The role of genetics in Parkinson's disease: a large cohort study in Chinese mainland population. Brain. 2020;143(7):2220-2234.
6. Marras C, Alcalay RN, Caspell-Garcia C, et al. Motor and nonmotor heterogeneity of LRRK2-related and idiopathic Parkinson's disease. Mov Disord. 2016;31(8):1192-1202.
7. Nalls MA, Blauwendraat C, Vallerga CL, et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet Neurol. 2019;18(12):1091-1102.
8. Pan H, Liu Z, Ma J, et al. Genome-wide association study using whole-genome sequencing identifies risk loci for Parkinson's disease in Chinese population. NPJ Parkinsons Dis. 2023;9(1):22.
9. Healy DG, Falchi M, O'Sullivan SS, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: a case-control study. Lancet Neurol. 2008;7(7):583-590.
10. Lesage S, Dürr A, Tazir M, et al. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. N Engl J Med. 2006;354(4):422-423.
11. Ozelius LJ, Senthil G, Saunders-Pullman R, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. N Engl J Med. 2006;354(4):424-425.
12. Pitz V, Makarious MB, Bandres-Ciga S, et al. Analysis of rare Parkinson's disease variants in millions of people. NPJ Parkinsons Dis. 2024;10(1):11.
13. Alcalay RN, Mirelman A, Saunders-Pullman R, et al. Parkinson disease phenotype in Ashkenazi Jews with and without LRRK2 G2019S mutations. Mov Disord. 2013;28(14):1966-1971.
14. Nabli F, Ben Sassi S, Amouri R, Duda JE, Farrer MJ, Hentati F. Motor phenotype of LRRK2-associated Parkinson's disease: a Tunisian longitudinal study. Mov Disord. 2015;30(2):253-258.
15. Oosterveld LP, Allen JC, Ng EYL, et al. Greater motor progression in patients with Parkinson disease who carry LRRK2 risk variants. Neurology. 2015;85(12):1039-1042.

16. Marder K, Wang Y, Alcalay RN, et al. Age-specific penetrance of LRRK2 G2019S in the Michael J. Fox Ashkenazi Jewish LRRK2 consortium. Neurology. 2015;85 (1):89-95.
17. Yahalom G, Orlev Y, Cohen OS, et al. Motor progression of Parkinson's disease with the leucine-rich repeat kinase 2 G2019S mutation. Mov Disord. 2014;29(8):1057-1060.
18. Cui S-S, Fu R, Du J-J, et al. Sex effects on clinical features in LRRK2 G2385R carriers and non-carriers in Parkinson's disease. BMC Neurosci. 2021;22(1):22.
19. Liang D, Shu L, Pan H, et al. Clinical characteristics of PD patients with LRRK2 G2385R and R1628P variants. Neurosci Lett. 2018;685:185-189.
20. Di W, Zeng Z, Li J, Liu X, Bo M, Lv H. The association between LRRK2 G2385R and phenotype of Parkinson's disease in Asian population: a meta-analysis of comparative studies. Parkinsons Dis. 2018;2018:3418306.
21. Lanore A, Casse F, Tesson C, et al. Differences in survival across monogenic forms of Parkinson's disease. Ann Neurol. 2023;94(1):123-132.
22. Thaler A, Kozlovski T, Gurevich T, et al. Survival rates among Parkinson's disease patients who carry mutations in the LRRK2 and GBA genes. Mov Disord. 2018;33 (10):1656-1660.
23. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55(3):181-184.
24. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord. 2015;30(12):1591-1601.
25. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12 (3):189-198.
26. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14 (6):540-545.
27. Shen S-S, Shen Y, Xiong K-P, et al. Validation study of REM sleep behavior disorder questionnaire-Hong Kong (RBDQ-HK) in east China. Sleep Med. 2014;15(8):952-958.
28. Yu Q, Guo P, Li D, et al. Olfactory dysfunction and its relationship with clinical symptoms of Alzheimer disease. Aging Dis. 2018;9(6):1084-1095.
29. Saunders-Pullman R, Mirelman A, Alcalay RN, et al. Progression in the LRRK2-asssociated Parkinson disease population. JAMA Neurol. 2018;75(3):312-319.
30. Simuni T, Brumm MC, Uribe L, et al. 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. Mov Disord. 2020;35(5):833-844.
31. Shu L, Zhang Y, Pan H, et al. Clinical heterogeneity among LRRK2 variants in Parkinson's disease: a meta-analysis. Front Aging Neurosci. 2018;10:283.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1.
Figure S2.
Captions.

