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ARTICLE

Comprehensive analysis of clinical and biological features in Parkinson's disease associated with the LRRK2 G2019S mutation: Data from the PPMI study

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Abstract

The Parkinson's Progression Marker Initiative (PPMI) aims to identify biomarkers for Parkinson's disease (PD) risk, onset, and progression. This study focuses on the G2019S missense mutation in the *LRRK2* gene, which is associated with hereditary and sporadic PD. Utilizing data from the PPMI database, we conducted an analysis of baseline clinical characteristics, as well as serum and cerebrospinal fluid levels in two groups: patients with PD with the G2019S mutation (PD + G2019S) and patients with PD without the mutation (PD-G2019S). Multiple linear regression and longitudinal analysis were performed, controlling for confounding factors. Compared to the PD-G2019S group, the PD + G2019S group showed more obvious initial motor dysfunction—higher baseline Movement Disorder Society-Sponsored Revision of the Unified Parkinson Disease Rating Scale (MDS-UPDRS) scores (false discovery rate [FDR]-adjusted $p < 0.001$), but progressed more slowly. Mechanism of Coordinated Access and activities of daily living (ADL) scores were lower at baseline (FDR-adjusted $p < 0.001$), whereas Scales for Outcomes of Parkinson's Disease (SCOPA)-Thermoregulatory (FDR-adjusted $p = 0.015$) scores were higher, emphasizing the increase of non-motor symptoms associated with LRRK2-G2019S mutation. During the follow-up period, the motor and non-motor symptoms changed dynamically with time, and there were longitudinal differences in the scores of MDS-UPDRS (FDR-adjusted $P_I = 0.013$, $P_{II} = 0.008$, $P_{IV} < 0.001$), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (FDR-adjusted $p = 0.027$), SCOPA-Thermoregulatory (FDR-adjusted $p = 0.021$), and ADL (FDR-adjusted $p = 0.027$) scale scores. PD associated with the LRRK2 G2019S mutation demonstrated more severe symptoms at baseline but slower progression. Motor complications and thermoregulatory disorders were more pronounced.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Current knowledge suggests that the LRRK2 G2019S mutation is a significant genetic factor associated with Parkinson's disease (PD). Studies have indicated that individuals with this mutation may present with distinct clinical features compared to non-carriers, but a comprehensive understanding of the varied aspects, including biomarkers and disease progression, is still evolving.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study aimed to comprehensively analyze PD associated with the LRRK2 G2019S mutation. The investigation delved into baseline characteristics, clinical and non-clinical symptoms, and longitudinal changes, addressing questions about the specific impact of the G2019S mutation on the clinical presentation, biomarker profiles, and disease progression in PD.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The study contributes novel insights into the clinical and biological features of PD related to the LRRK2 G2019S mutation. It confirms existing knowledge that individuals with this mutation exhibit more severe symptoms at baseline, such as higher Movement Disorder Society-Sponsored Revision of the Unified Parkinson Disease Rating Scale scores and impaired cognition. Surprisingly, it adds the finding that these individuals experience a slower rate of disease progression, particularly in motor complications, suggesting potential compensatory mechanisms.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These findings hold potential implications for clinical practice and translational research. Understanding the distinct characteristics of PD with the G2019S mutation could lead to more personalized treatment approaches. The identification of specific biomarker trends, even if preliminary, opens avenues for further research into targeted therapies. The slower disease progression observed challenges and assumptions about the linear nature of the mutation's effects, highlighting the need for nuanced approaches in clinical pharmacology tailored to the genetic profile of patients with PD. Overall, this study provides a foundation for refining intervention strategies and emphasizes the importance of considering genetic factors in PD research and treatment.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease.[1] It is characterized by motor symptoms, such as bradykinesia, rigidity, resting tremor, and postural instability, as well as non-motor symptoms, including olfactory disturbances, sleep disturbances, cognitive impairments, psychiatric symptoms, autonomic dysfunction, pain, and fatigue.[2] Both environmental exposures and genetic factors, including mutations in the leucine-rich repeat kinase 2 (*LRRK2*) gene, contribute to the development of PD.[3]

The clinical and non-motor manifestations of PD vary among individuals with LRRK2 mutations, and the findings from previous studies have been inconsistent. Whereas most LRRK2 carriers present with late-onset PD that is clinically similar to non-carriers,[4] here are certain distinct features observed. LRRK2-associated PD generally follows a more benign course,[5] exhibits relatively preserved olfactory function and milder cognitive deficits compared to idiopathic PD,[6] and shows a lower prevalence of rapid eye movement (REM) sleep behavior disorder (RBD) and excessive daytime sleepiness.[7,8] However, LRRK2 carriers may have a higher prevalence of tremor,[9] lower executive function,[10] and more frequent insomnia.[7] Additionally, atypical features, such as dementia, hallucinations, primary progressive aphasia, and orthostatic hypotension, have been reported.[4] The most prevalent LRRK2 mutation is Gly2019Ser (G2019S, rs34637584).[11,12]

Existing studies have suggested that G2019S carriers, who are predominantly women, tend to have lower rates of depression and hyposmia, as well as better self-care abilities. They also exhibit a positive response to levodopa treatment but require higher daily doses and are more likely to experience motor complications.[13] However, most of these studies have focused either on cross-sectional analyses or longitudinal survival analyses, leaving a gap in comprehensive investigations combining both approaches to compare patients with PD with and without LRRK2 mutations. Integrating these methods would yield a holistic understanding of LRRK2 mutation impacts on PD, spanning from diagnosis throughout the disease course. LRRK2, a serine/threonine kinase within the ROCO protein family, exhibits heightened activity due to the G2019S mutation.[14] LRRK2 is a key player in cell signaling and influences autophagy,[15,16] apoptosis,[17] mitochondrial function,[18] and neuroinflammation.[14,19] Given the age-associated nature of LRRK2-mediated disease, we hypothesize a later onset of PD symptoms.[20] This distinct presentation may manifest unique motor and non-motor symptoms and potentially discernible biomarkers in cerebrospinal fluid (CSF) and serum. Thus, studying distinct clinical features and biomarkers in LRRK2-linked PD is crucial.

The Parkinson's Disease Progression Marker Initiative (PPMI) database, with its extensive genetic information and comprehensive assessments, provides an excellent resource for investigating these aspects in a large cohort of PD participants.[21] In this study, our objectives were to examine whether patients with PD carrying the LRRK2-G2019S mutation display distinctive clinical, serum, and CSF characteristics compared to those with idiopathic PD, and to explore the potential of clinical, genetic, blood, and CSF biomarkers for assessing disease progression in PD. The findings from our study could contribute to a better understanding of the genetic basis of PD and facilitate the development of targeted treatment approaches.

MATERIALS AND METHODS

Study design

The PPMI database was utilized to access demographic information, clinical data, and biomarker data of the participants[22] (http://www.ppmi-info.org/data). Standardized scales from the PPMI database were used for the assessment of clinical symptoms. Statistical analysis was conducted to examine the clinical significance of mutations in the G2019S locus of the *LRRK2* gene, which is commonly observed in PD. Unlike previous cross-sectional analyses, this study goes beyond baseline comparisons and includes a longitudinal extension, allowing for a comprehensive evaluation of participants within the PPMI cohort. Emphasis was placed on understanding the long-term impact of this mutation on patients with PD, exploring the relationship between disease progression and the mutation, and providing insights for future clinical interventions. The experimental strategy and workflow are illustrated in Figure 1.

Participants

Our study utilized data collected from the PPMI database, spanning from June 2010 to April 2020. Due to the impact of the coronavirus disease 2019 (COVID-19) pandemic, no additional data were added during this period. We want to clarify that the inclusion and exclusion criteria for our study were derived from the original PPMI study. The inclusion criteria for patients with PD were as follows: (1) both men and women aged 30 years or older at enrollment; (2) PD diagnosis within the last 2 years; (3) Hoehn and Yahr stage I, II, or III at enrollment; (4) no PD medication for at least 6 months following inclusion in the PPMI study; (5) female participants should not be planning to become pregnant, are pregnant, or breastfeeding during the study period; and (6) eligibility confirmation based on Screening DaTscan imaging.

To ensure the focus of our study on the G2019S mutation in the *LRRK2* gene, we excluded 83 subjects with missing genetic test information and those with *LRRK2* gene mutations other than the G2019S mutation from the PPMI dataset. As a result, we currently retain baseline and follow-up data on clinical, serum, and CSF features of 883 newly diagnosed patients with PD, including 275 patients with PD with the LRRK2 G2019S mutation.

Data source

Our studies heavily rely on clinical assessments, evaluations, subject demographics, and biological samples obtained from the PPMI dataset. These data results are obtained from PPMI upon request and after approval by the PPMI Data Access Committee. The PPMI study has implemented standardized procedures and rigorous quality control measures for data acquisition, transmission, and analysis, as well as for the collection, processing, and storage of biospecimens. These standardized protocols aim to ensure consistency and minimize variability across the dataset (Figure S1). Detailed information regarding the specific research proposals and study design can be accessed at www.ppmi-info.org/study-design.

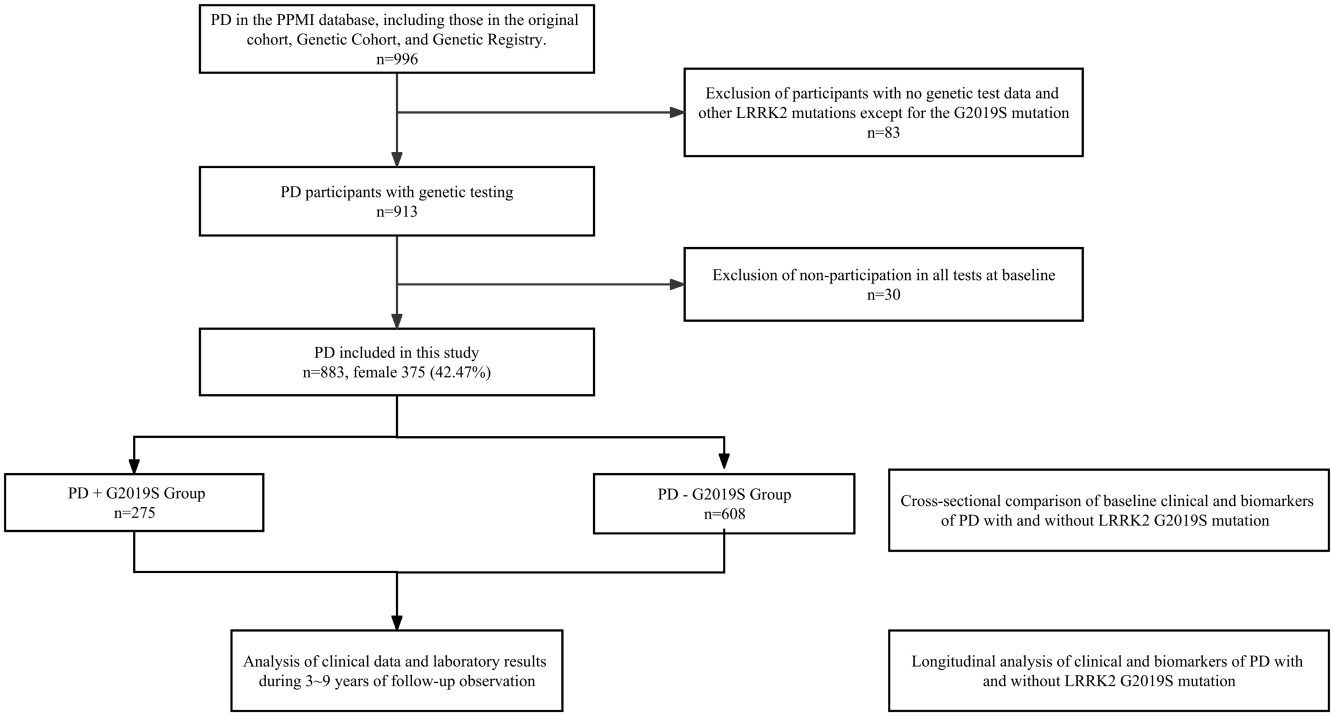

FIGURE 1 Experimental strategy and workflow. PD, Parkinson's disease; PPMI, Parkinson's Progression Marker Initiative.

Outcomes

All participants in the PPMI study underwent whole exome or genome sequencing, which included testing for various mutations in the *LRRK2* gene, including G2019S, R1441G/C, G2385R, R1628P/H, and Y1699C. For the purpose of this study, we specifically focused on the most common G2019S mutation. Baseline demographic variables, such as sex, age, education, race, ethnicity, and family history, were collected from the PPMI dataset. Clinical data included assessments of motor symptoms, non-motor symptoms, and neurobehavioral function. These tools included the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)[23] Parts I-IV, Hopkins Verbal Learning Test,[24,25] Benton Judgment of Line Orientation Test,[26] Semantic Fluency Test,[27] Letter Number Sequencing,[28] Symbol Digit Modalities Test,[29] Montreal Cognitive Assessment (MoCA),[30] Geriatric Depression Scale,[31] State–Trait Anxiety Inventory,[32] Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP),[33] Scales for Outcomes in Parkinson's Disease – Autonomic (SCOPA-AUT),[34] Epworth Sleepiness Scale,[35] rapid eye movement (REM) Sleep Behavior Disorder Screening Questionnaire,[36] University of Pennsylvania Smell Identification Test,[37,38] and Activities of Daily Living (ADL).[39] (Table 1). Furthermore, biomarkers such as serum uric acid, serum neurofilament light chain (NFL), and CSF levels of αSynuclein, Aβ1-42, total tau (t-tau), phosphorylated tau (p-tau$_{181}$), and NFL were analyzed.

Statistical analysis

Descriptive statistics were used to represent the baseline features of participants, with continuous variables expressed as means (standard deviations) and categorical variables expressed as numbers. We conducted the Kruskal–Wallis test and χ^2 test to compare baseline demographic data of different subgroups. In the cross-sectional analysis, multiple linear regression analysis was performed for clinical data and biomarkers with the presence or absence of the LRRK2 G2019S mutation as the independent variable, while adjusting for covariates, including age, sex, race, education level, and family history, respectively. For the longitudinal analysis, a linear mixed-effects model was developed to assess the effect of the LRRK2 G2019S mutation on clinical features and biomarkers in PD during 3–9 years of follow-up (the specific follow-up years and the number of cases per follow-up are shown in the table for Supplementary Materials). Age, sex, race, education level, family history, and levodopa equivalent daily dose (LEDD) were included as covariates. We performed a collinearity analysis for all variables, and the results (Table S2) showed a low variance inflation factor value, indicating a low correlation between variables and possibly a small collinearity effect. Additionally, we conducted subgroup analyses by sex to compare whether the effects caused by the LRRK2 G2019S mutation would differ among patients with PD by sex. For all models, the false discovery rate (FDR) was controlled by adjusting the

TABLE 1 Motor and non-motor assessments.

Assessment tool	Clinical assessments	Description
MDS-UPDRS	Movement Disorder Society-Sponsored Revision Unified Parkinson's Disease Rating Scale	Higher scores indicate more advanced Parkinson's disease
Part I	Non-Motor Aspects of Experiences of Daily Living (N-EDL)	Higher scores indicate greater impact on non-motor aspects of daily living
Part II	Motor Aspects of Experiences of Daily Living (M-EDL)	Higher scores suggest increased motor difficulties in daily activities
Part III	Motor Examination	Higher scores indicate more severe motor symptoms and impairments
Part IV	Motor Complications	Higher scores suggest greater motor complications and side effects
HVLT	Hopkins Verbal Learning Test	Higher scores indicate better verbal learning and memory
BJLOT	Benton Judgment of Line Orientation Test	Higher scores indicate better spatial orientation and visuospatial skills
SFT	Semantic Fluency Test	Higher scores indicate better semantic fluency and cognitive flexibility
LNS	Letter Number Sequencing	Higher scores indicate better working memory and attention
SDMT	Symbol Digit Modalities Test	Higher scores indicate better processing speed and attention
MoCA	Montreal Cognitive Assessment	Scores ≥26 are considered normal; lower scores suggest cognitive impairment
GDS	Geriatric Depression Scale	GDS ≥5 are "Depressed" GDS <5 are "Not Depressed"
STAI	State–Trait Anxiety Inventory	Higher scores indicate higher levels of anxiety
QUIP	Questionnaire for Impulsive	Higher scores indicate more severe impulse control disorder
SCOPA-AUT	Scales for Outcomes in Parkinson's disease – Autonomic	Higher scores indicate more severe autonomic dysfunction
Gastrointestinal	SCOPA-AUT: Gastrointestinal Component	Higher scores indicate more severe autonomic dysfunction in the gastrointestinal system
Urinary	SCOPA-AUT: Urinary Component	Higher scores indicate more severe autonomic dysfunction in the urinary system
Cardiovascular	SCOPA-AUT: Cardiovascular Component	Higher scores indicate more severe autonomic dysfunction in the cardiovascular system
Pupillomotor	SCOPA-AUT: Pupillary Motility Component	Higher scores indicate more severe autonomic dysfunction in pupillary motility
Thermoregulatory	SCOPA-AUT: Thermoregulation Component	Higher scores indicate more severe autonomic dysfunction in thermoregulation
Sexual dysfunction	SCOPA-AUT: Sexual Function Component	Higher scores indicate more severe autonomic dysfunction in sexual function
ESS	Epworth Sleepiness Scale Score	ESS <10 are "Not Sleepy" ESS ≥10 are "Sleepy"
RBDSQ	Rapid-eye-movement sleep Behavior Disorder questionnaire	<5 are "No RBD" ≥5 are "RBD"
UPSIT	University of Pennsylvania Smell Identification Test	Higher scores indicate better olfactory function
ADL	Modified Schwab & England ADL Score	Higher scores indicate better self-care ability

p values using the Benjamini and Hochberg methods, ensuring that the statistical significance of the reports was robust and that the risk of false positives was minimized. Statistical analyses were performed using R 4.2.0, and the adjusted p value < 0.05 was considered statistically significant.

Ethics statement

The PPMI study collected participant data in full accordance with Good Clinical Practice and International Coordination Conference guidelines and any applicable national and local regulations. All participating PPMI sites obtained local institutional review board or independent ethics committee approval for human experimentation prior to the start of the study and obtained informed written consent from all participants in the study. More information is available at https://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites.

RESULTS

Characterization of participants at baseline

The demographic features of the participants are summarized in Table 2. The study included 883 PD participants, consisting of 275 individuals with the LRRK2 G2019S mutation (PD + G2019S group) and 608 individuals without the LRRK2 mutation (PD-G2019S group). The two groups had similar distributions in terms of race and educational attainment, with no statistically notable differences observed (FDR-adjusted $p > 0.050$). Notably, if less conservative and more focused on comprehensiveness, the PD + G2019S group appears to have a higher proportion of White individuals ($q = 0.047$). The PD + G2019S group had a higher average age, suggesting a later onset of PD (FDR-adjusted $p < 0.001$). Moreover, the percentage of women in the PD + G2019S group statistically exceeded that in the PD-G2019S group (50.90% vs. 38.65%, FDR-adjusted $p < 0.001$), suggesting a potential gender association. There was also a notable difference in the prevalence of affected relatives, suggesting a stronger familial heritability in the PD + G2019S group (FDR-adjusted $p < 0.001$).

Cross-sectional analysis of PD with and without the LRRK2 G2019S mutation

Heatmap showing the results of cross-sectional analysis of PD with and without LRRK2 G2019S mutation (Figure 2).

Baseline assessment of motor symptoms and non-motor symptoms

In the baseline assessment of the entire PD population, the PD + G2019S group showed the following characteristics compared with the PD-G2019S group. They had higher MDS-UPDRS scores in all sections of the scale ($\beta = 6.316$, FDR-adjusted $p < 0.001$; $q < 0.001$), indicating heavier motor impairment. Lower scores were on the MoCA scale ($\beta = -1.628$, FDR-adjusted $p < 0.0011$; $q < 0.001$) and higher scores on the thermoregulation in SCOPA-AUT ($\beta = 0.553$, FDR-adjusted $p = 0.015$, $q = 0.0048$) indicated more severe non-motor symptoms, including cognitive impairment and impairment of thermoregulation function. Lower modified Schwab and& England ADL scores ($\beta = -4.522$, FDR-adjusted $p < 0.001$, $q < 0.001$) reflect greater difficulties in daily activities and quality of life.

It is worth noting that in the gender analysis, only the male PD + G2019S group exhibited notably higher MDS-UPDRS I, II, III scores and QUIP scores than the same-sex PD-G2019S group (FDR-adjusted $p < 0.005$, $q < 0.005$). It is suggested that the G2019S mutation mainly causes the male patients with PD to have worse motor status and impulse control disorder at baseline. However, we observed that the average QUIP score may not be indicative enough to diagnose impulse control disorder. Therefore, this difference may not necessarily hold clinical relevance (Figure 3).

Baseline assessment of biomarkers

In our analysis of biomarkers, we observed that serum NFL levels were notably higher in the male PD + G2019S group compared to the male PD-G2019S group ($\beta = 0.063$, FDR-adjusted $p = 0.046$, $q = 0.046$). We further performed multiple linear regression analysis using the ratio of metabolites and identified differences in serum NFL/CSF $A\beta_{1-42}$ ($p = 0.021$) and in PD between the two groups. In male patients with PD, differences in serum NFL/CSF $A\beta_{1-42}$ ($p = 0.040$), CSF p-tau_{181}/CSF $A\beta_{1-42}$ ($p = 0.003$), CSF t-tau/ CSF $A\beta_{1-42}$ ($p = 0.007$) and CSF p-tau_{181}/CSF t-tau ($p = 0.025$) were also confirmed. However, it is crucial to note that after applying FDR correction to account for multiple testing, the adjusted p values > 0.05. The initially observed differences should be interpreted with caution, as they did not withstand the correction for multiple testing. These particular findings should be viewed as exploratory, and further validation or replication studies may be warranted to confirm the observed trends.

Longitudinal analysis of PD with and without the LRRK2 G2019S mutation

In our longitudinal analysis, we evaluated the effect of LRRK2 G2019S mutations on clinical symptoms and biomarker development of PD using a linear mixed-effects model (Figure 2). We created two different linear mixed-effect models, one that included LEDD as a covariable, whereas the other excluded LEDD to explore its potential

TABLE 2 Baseline characteristics of participants.

	PD + G2019S (*N* = 275)	PD − G2019S (*N* = 608)	*p* Value	*FDR-p* value	*Q* value
Patient characteristics					
Age at baseline, mean (SD)	66.5 (10.7)	62.5 (10.2)	**1.857e^{-07}**	**1.41e^{-06}**	**7.11e^{-07}**
Sex, number (percentage)					
Male	135 (49.1)	373 (61.3)	**0.0008**	**0.0030**	**0.0015**
Female	140 (50.9)	235 (38.7)			
Race, number (percentage)					
White	266 (96.7)	564 (92.8)	**0.0321**	0.0938	**0.0472**
Other	9 (3.3)	44 (7.2)			
Education, mean (SD)	15.6 (4.1)	15.5 (3.5)	0.2993	0.3987	0.2008
Family history of PD in first-degree relative, number (percentage)					
Yes	126 (45.8)	143 (23.5)	**2.462e^{-11}**	**4.68e^{-10}**	**2.36e^{-10}**
No	146 (53.1)	463 (76.2)			
Family history of PD, number (percentage)					
Yes	170 (61.8)	214 (35.2)	**1.041e^{-13}**	**3.96e^{-12}**	**1.99e^{-12}**
No	102 (37.1)	392 (64.8)			
Clinical characteristics					
MDS-UPDRS Total Score, mean (SD)	44.2 (22.7)	36.13 (18.1)	**3.444e^{-07}**	**2.18e^{-06}**	**1.10e^{-06}**
MDS-UPDRS I Score, mean (SD)	8.9 (5.9)	6.87 (5.4)	**1.105e^{-07}**	**1.05e^{-06}**	**5.29e^{-07}**
MDS-UPDRS II Score, mean (SD)	10.1 (8.3)	7.15 (5.8)	**6.096e^{-07}**	**3.31e^{-06}**	**1.67e^{-06}**
MDS-UPDRS III Score, mean (SD)	25.1 (12.9)	22.11 (11.0)	**0.0013**	**0.0045**	**0.0023**
MDS-UPDRS IV Score, mean (SD)	2.5 (3.5)	2.27 (3.1)	0.8587	0.9064	0.4564
HVLT Score, mean (SD)	24.9 (4.7)	24.09 (5.3)	0.3043	0.3987	0.2008
BJLOT Score, mean (SD)	12.1 (2.5)	12.3 (2.6)	0.0837	0.1767	0.0890
SFT Score, mean (SD)	50.4 (12.4)	48.3 (12.3)	**0.0360**	0.0955	0.0481
LNS Score, mean (SD)	10.1 (2.5)	10.2 (2.9)	0.5419	0.6643	0.3345
SDMT Score, mean (SD)	40.5 (11.1)	40.0 (10.8)	0.9878	0.9878	0.4974
MoCA Score, mean (SD)	24.8 (4.3)	26.7 (3.1)	**9.798e^{-08}**	**1.05e^{-06}**	**5.29e^{-07}**
GDS Score, mean (SD)	2.9 (2.9)	2.7 (2.9)	0.2559	0.3602	0.1813
STAI Score, mean (SD)	69.6 (19.2)	67.6 (19.4)	0.08336	0.1767	0.0890
QUIP Score, mean (SD)	0.5 (0.9)	0.4 (0.7)	**0.0377**	0.0955	**0.0481**
SCOPA-AUT Score, mean (SD)	12.1 (8.0)	10.6 (7.1)	**0.0143**	**0.0453**	**0.0228**
Gastrointestinal	2.82 (2.9)	2.6 (2.5)	0.7506	0.8149	0.4103
Urinary	4.83 (3.5)	4.5 (3.3)	0.1808	0.2987	0.1504
Cardiovascular	0.71 (1.0)	0.6 (0.9)	0.1213	0.2128	0.1071
Pupillomotor	0.5 (0.9)	0.4 (0.6)	0.6266	0.7215	0.3633
Thermoregulatory	2.1 (2.4)	1.4 (1.8)	**0.0004**	**0.0017**	**0.0009**
Sexual dysfunction	1.1 (1.7)	1.1 (1.6)	0.9263	0.9513	0.4790
Epworth Sleepiness Scale Score, mean (SD)	6.4 (4.4)	6.2 (3.9)	0.5665	0.6727	0.3387
RBD Questionnaire Score, mean (SD)	3.9 (2.6)	4.3 (2.9)	0.1232	0.2128	0.1071
UPSIT Score, mean (SD)	22.8 (8.2)	21.9 (8.2)	0.1140	0.2128	0.1071
Modified Schwab & England ADL Score, mean (SD)	85.2 (17.8)	90.9 (9.9)	**0.0002**	**0.0010**	**0.0005**

(Continues)

TABLE 2 (Continued)

	PD + G2019S ($N = 275$)	PD − G2019S ($N = 608$)	*p* Value	*FDR-p* value	*Q* value
Biomarker characteristics					
Serum uric acid (μmol/L), mean (SD)	274.8 (97.4)	318.4 (78.6)	0.1939	0.3063	0.1542
Serum NFL (pg/mL), mean (SD)	15.7 (11.4)	13.5 (7.6)	0.0973	0.1946	0.0980
CSF α-synuclein (pg/mL), mean (SD)	220.1 (291.6)	787.5 (826.1)	0.2235	0.3267	0.1645
CSF Aβ1-42 (pg/mL), mean (SD)	852.4 (414.9)	902.2 (401.2)	0.0805	0.1767	0.0890
CSF t-tau (pg/mL), mean (SD)	178.5 (58.0)	168.4 (56.9)	0.4992	0.6323	0.3184
CSF p-tau (pg/mL), mean (SD)	16.4 (4.8)	14.7 (5.2)	0.2015	0.3063	0.1542
CSF NFL (pg/mL), mean (SD)	86.9 (24.5)	103.2 (58.5)	0.7116	0.7953	0.4005

Note: Descriptive statistics were used to represent the baseline features of participants, with continuous variables expressed as means (standard deviations) and categorical variables expressed as numbers. We conducted the Kruskal–Wallis test and χ^2 test to compare baseline demographic data of different subgroups. The Benjamini and Hochberg method is used to control the error detection rate (FDR) by adjusting the *p* values. The adjusted *p* values and *q* values are also listed in the table.

Abbreviations: ADL, Activity of Daily Living Scale; BJLOT, Benton Judgment of Line Orientation Test; CSF, cerebrospinal fluid; FDR, false discovery rate; GDS, Geriatric Depression Scale; HC, healthy control; HVLT, Hopkins Verbal Learning Test; LNS, Letter Number Sequencing; MDS-UPDRS, Movement Disorder Society-Sponsored Revision Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; NFL, neurofilament light chain; PD, Parkinson's disease; QUIP, Questionnaire for Impulsive; RBD, Rapid-eye-movement sleep Behavior Disorder; SCOPA-AUT, Scales for Outcomes in Parkinson's disease – Autonomic; SDMT, Symbol Digit Modalities Test; SFT, Semantic Fluency Test; STAI: State–Trait Anxiety Inventory; UPSIT, University of Pennsylvania Smell Identification Test.

impact on the results. It is important to note that our LEDD follow-up data are limited by sample size. Therefore, we performed a sensitivity analysis to assess the potential impact of LEDD on the results of our model. Importantly, the results of the sensitivity analysis showed that whether we included or excluded LEDD did not have a statistically discernible effect on the results of the study.

Therefore, in our final model, we deliberately chose to exclude LEDD as a covariable. This decision was made to ensure the reliability and interpretability of the model, especially in light of the limitations on subsequent LEDD data. These analyses played a crucial role in confirming the results of our cross-sectional analysis and providing valuable insights into the long-term effects of LRRK2 G2019S mutations in patients with PD.

Longitudinal assessment of motor symptoms and non-motor symptoms

In our analysis of motor symptoms in PD, we observed noteworthy longitudinal differences between the PD + G2019S and PD-G2019S groups. The PD + G2019S group exhibited a smoother progression with slower decline in MDS-UPDRS scores compared to the PD-G2019S group. Specifically, notable differences were observed in the mental, behavioral, and emotional tests of part I ($\beta = 0.238$, FDR-adjusted $p = 0.013$), motor symptoms of daily life in the part II ($\beta = 0.254$, FDR-adjusted $p = 0.008$), and motor complications in the part IV ($\beta = 0.254$, FDR-adjusted $p < 0.001$) of the MDS-UPDRS scale. However, there was no statistically meaningful difference between the two groups in the longitudinal prediction of part III, which evaluates the physician's score of the exercise examination of the patient.

In relation to non-motor symptoms, QUIP scores in the PD + G2019S group exhibited a noteworthy downward trend with the increase of disease duration, whereas the scores in the PD-G2019S group increased gradually ($\beta = 0.041$, FDR-adjusted $p = 0.027$), with crossover at the fourth year of follow-up. These results indicated that although the PD-G2019S group initially had a higher impulse control disorder score than the PD + G2019S group, it gradually decreased, but PD impulse control disorder without mutation gradually worsened, but this difference may not be clinically noteworthy. When the autonomic nervous system was evaluated by the SCOPA-AUT scale, it was found that the increase of thermoregulatory score in the PD + G2019S group was faster ($\beta = 0.291$, FDR-adjusted $p = 0.021$), suggesting that the mutant group had more and more serious thermoregulation disorder. Additionally, ADL scores ($\beta = -0.203$, FDR-adjusted $p = 0.027$) declined more slowly over time in the PD + G2019S group than in the PD-G2019s group. After 2.5 years of follow-up, the self-care ability and quality of life of the non-mutant group were gradually worse than that of the mutant group (Figure 4).

In our subgroup analysis according to gender, we observed longitudinal differences in the female group in part IV ($\beta = 0.633$, FDR-adjusted $p < 0.001$) of the MDS-UPDRS scale, indicating differences in motor complications over time, with faster progression in the PD-G2019S

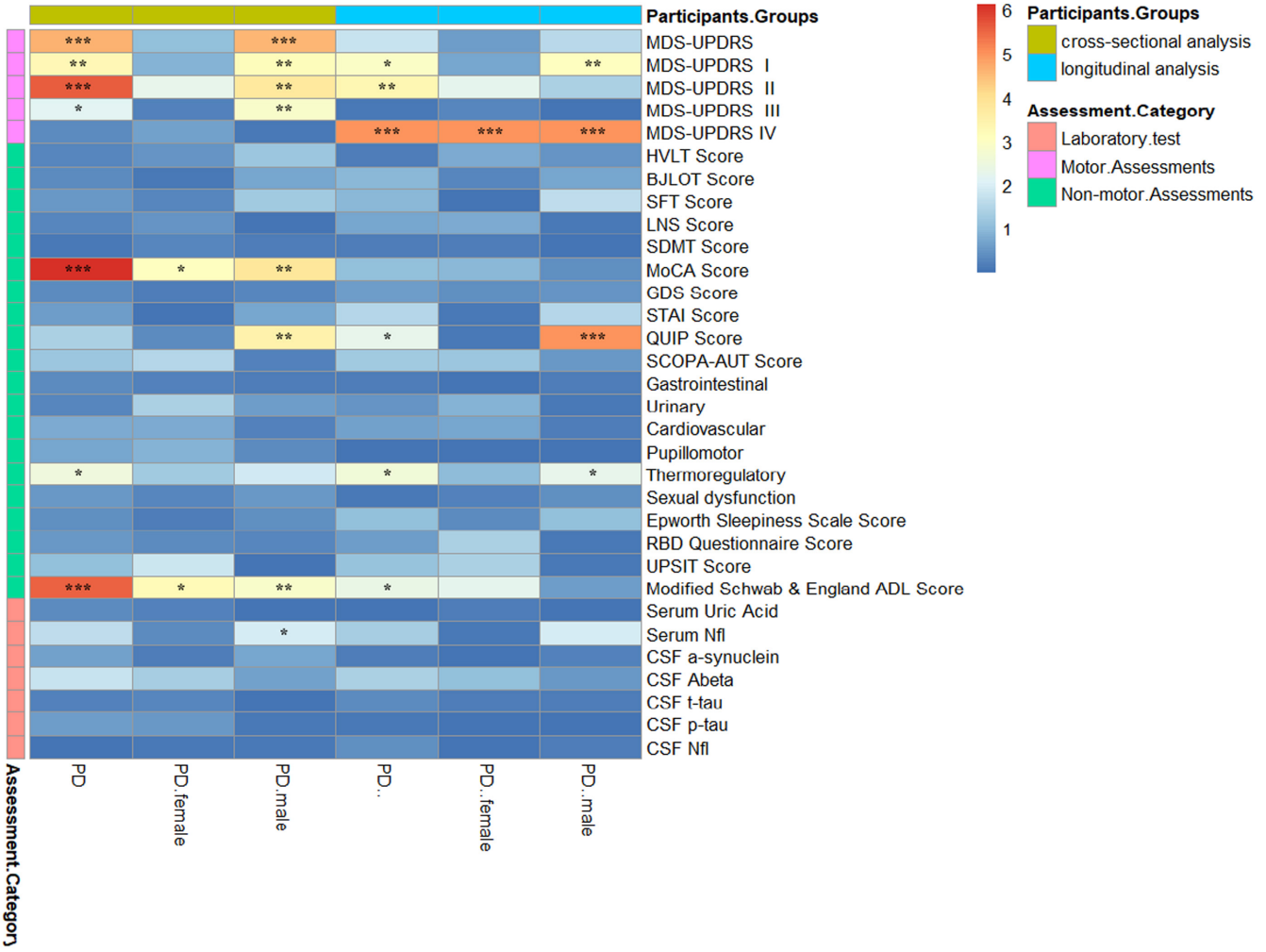

FIGURE 2 Results of the cross-sectional analysis and longitudinal analysis of PD with and without LRRK2 G2019S mutation represented by heat maps. Heat is expressed using visualized FDR-adjusted *p*-values (−log10, *p* value). Visualized FDR-adjusted *p* values ≥ −1.3 correspond to *p* values < 0.05. If the FDR-adjusted *p* value is significant, it is indicated with an asterisk in the relevant heatmap: *** 0.001, **0.01, * 0.05. ADL, activities of daily living; BJLOT, Benton Judgment of Line Orientation Test; FDR, false discovery rate; GDS, Geriatric Depression Scale; HVLT, Hopkins Verbal Learning Test; MDS-UPDRS, Movement Disorder Society-Sponsored Revision of the Unified Parkinson Disease Rating Scale; MoCA, Mechanism of Coordinated Access; PD, Parkinson's disease; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; RBD, rapid eye movement (REM) sleep behavior disorder; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease – Autonomic; SDMT, Symbol Digit Modalities Test; SFT, Semantic Fluency Test; STAI, State–Trait Anxiety Inventory; UPSIT, University of Pennsylvania Smell Identification Test.

group. For the male subgroup, the differences in MDS-UPDRS part I, IV, QUIP, and SCOPA-Thermoregulatory scale scores were comparable to the overall PD analysis.

Longitudinal assessment of biomarkers

In our longitudinal analysis of biomarkers, before FDR correction we observed differences between the PD + G2019S and PD-G2019S groups. CSF $A\beta_{1-42}$ levels were consistently lower in the PD + G2019S group compared to the PD-G2019S group throughout the follow-up period ($\beta = -0.263$, $p = 0.041$). In the male subgroup, we observed that serum NFL levels were consistently higher in the PD + G2019S group compared to the PD-G2019S group, and this difference increased over time ($\beta = 0.256$, $p = 0.012$), indicating potential neuronal damage or neurodegeneration associated with the LRRK2 G2019S mutation. Unfortunately, after FDR correction, these differences do not exist.

DISCUSSION

Our study offers a comprehensive analysis of PD associated with the LRRK2 G2019S mutation, shedding light on the clinical and biological characteristics of this specific genetic variant. Through our investigation, we identified

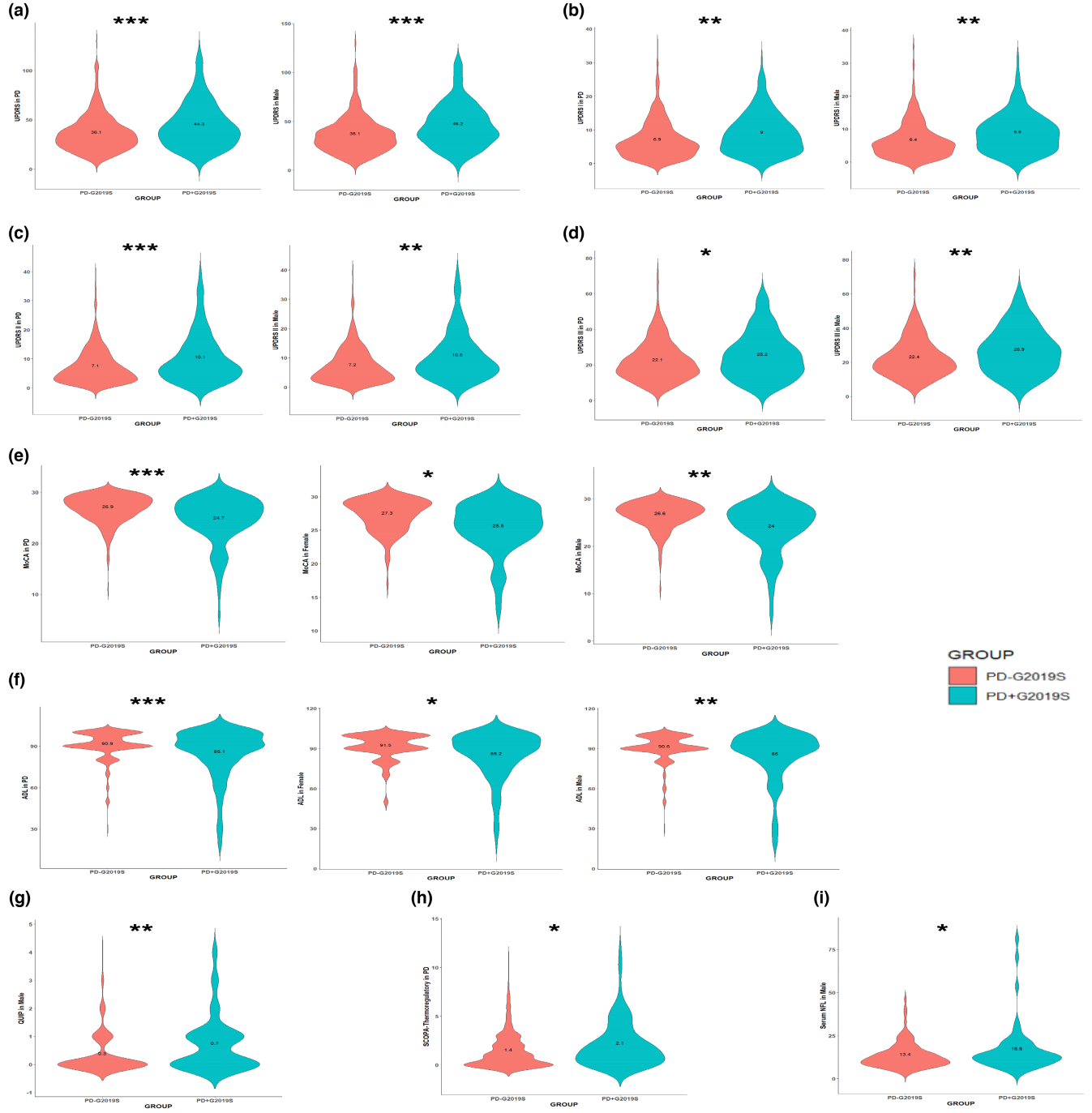

FIGURE 3 Differences in baseline assessments. It mainly shows the difference in baseline assessment between the two groups, using a violin chart. Each violin diagram represents a different group (light red represents the PD-G2019S group, cyan represents PD + G2019S group.) The horizontal axis represents the groups and the vertical axis represents the different assessment items. The average value is represented by a label. (a–d) Baseline UPDRS scores (I, II, III) were lower in the whole PD + G2019S group compared to the whole PD-G2019S group, particularly in the male subgroup. (e) Baseline cognitive levels (MoCA) and (f) ability to perform ADL were lower in the whole PD + G2019S group, with notably differences observed in both men and women. (g) Baseline QUIP scores were higher in the male PD + G2019S group. (h) Baseline thermoregulatory function was worse in the whole PD + G2019S group. (i) Baseline serum NFL levels were higher in the male PD + G2019S group. Significance levels for FDR-adjusted *p* values are denoted by asterisks: '***' 0.001, '**' 0.01, '*' 0.05. ADL, activities of daily living; FDR, false discovery rate; MoCA, Montreal Cognitive Assessment; NFL, Neurofilament Light Chain; PD, Parkinson's Disease; QUIP, Questionnaire for Impulsive; UPDRS, Unified Parkinson's Disease Rating Scale.

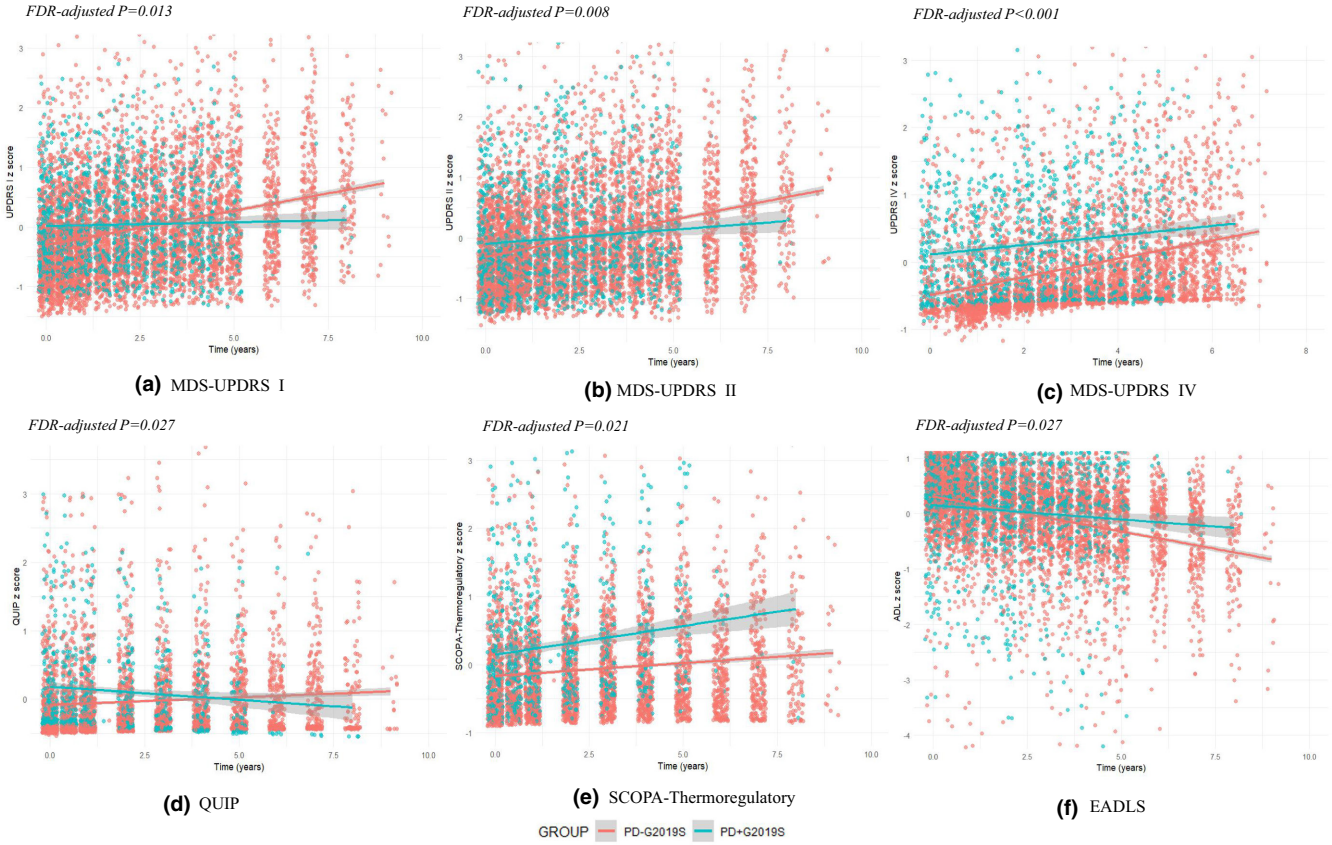

FIGURE 4 Longitudinal analysis of clinical indicator changes. Mainly to show the difference in longitudinal assessment between the two groups in overall PD, we fit the scatter plot with linear regression (light red for the PD-G2019s group, cyan for the PD + G2019S group). The *X*-axis represents follow-up years, and the *Y*-axis represents standardized predictions of different scale scores. (a) MDS-UPDRS I *z* scores increased slowly in the PD + G2019S group compared to the PD-G2019S group during the 9-year follow-up, with crossover points over time. (b) MDS-UPDRS II *z* scores exhibited a similar trend, showing a slow increase in the PD + G2019S group compared to the PD-G2019S group. (c) MDS-UPDRS IV *z* scores also increased gradually in the PD + G2019S group over the 9-year period, with no crossover observed at present, but it was expected. (d) QUIP *z* scores decreased slowly in the PD + G2019S group over time, exhibiting crossover points, while the PD-G2019S group showed an increase. (e) The thermoregulation *z* score of SCOPA in the PD + G2019S group increased year by year, surpassing that in the PD-G2019S group. (f) The ADL *z* score of the PD + G2019S group declined slowly, with observed crossover points. EADLS, English Activities of Daily Living Scale; FDR, false discovery rate; MDS-UPDRS, Movement Disorder Society-Sponsored Revision Unified Parkinson's Disease Rating Scale; PD, Parkinson's Disease; QUIP, Questionnaire for Impulsive; SCOPA, Scales for Outcomes of Parkinson's Disease; *z* score, standardized score.

several key findings that advance our understanding of LRRK2-associated PD.

Our findings confirm the notion that individuals with the LRRK2 G2019S mutation exhibit a more severe clinical presentation at the baseline.[5,13,40–45] This was evident from their higher MDS-UPDRS scores, lower MoCA scores, and impaired thermoregulation, impulse control, and self-care abilities. These observations are consistent with prior research but also reveal nuanced differences. Although these baseline differences may not be sufficient to lead to clinically meaningful changes, they may be differentiated over time. The slower rate of disease progression in LRRK2 G2019S carriers, accompanied by a reduction in impulse control problems, was a surprising finding. This may involve complex compensatory mechanisms and cellular repair processes that may help slow disease progression. This observation suggests that the effect of G2019S mutations on the disease process may not be just linear, but influenced by multiple factors. The variability in disease progression among different populations suggests that further exploration is needed.[6,46–48] This may involve the interaction of genetic, environmental, and other unknown factors that have a complex effect on disease progression in LRRK2 G2019S carriers. Therefore, we emphasize the importance of studying small effect sizes to more fully understand these subtle differences and provide more precise protocols for future interventions and treatments.

The underlying mechanism for this phenomenon is not yet fully understood, and it remains important to

investigate whether G2019S carriers experience a longer diagnostic delay, which could contribute to their later disease onset. Although all participants in our study were recruited within 2 years of diagnosis, variations in actual disease duration between the two groups may impact the comparisons. The delayed age of onset in G2019S carriers has not been reported in current literature, and we hypothesize that G2019S carriers may experience longer diagnostic delays, leading to a later disease onset. However, further research is needed to explore and explain this phenomenon. It has been suggested that the absence of notable differences in disease progression between the two groups may be attributed to a "ceiling effect" in the mutant group, where their baseline symptoms are already extremely severe, leaving limited room for further progression. However, our analysis indicates that the likelihood of such a situation is not high. Although the baseline symptoms in the mutation group are indeed severe, it appears that they may not reach a peak state. Therefore, additional investigation is warranted to elucidate the factors influencing disease progression in individuals with the G2019S mutation.

In terms of sex differences,[13,45,49] in men, the presence of the G2019S mutation was associated with lower motor capacity, cognition, and quality of life, and higher QUIP and thermoregulatory disorder scores showed that motor symptoms, cognitive impairment, and thermoregulation deficits were more severe in the mutant group than in the male non-mutant group at baseline. Although these dysfunctions progressed more rapidly in the non-mutant group, they often surpassed the mutant group by the end of follow-up. The clinical significance of these small effects may lie in the fact that mutation carriers exhibit more pronounced impairments in motor and cognitive function and more severe thermoregulation problems in the earlier stages of the disease. Although these differences decreased over the course of follow-up, they still shed light on specific aspects of G2019S mutations in men with PD, contributing to a better understanding of the relationship between G2019S mutations and disease presentation, and providing a basis for individualized treatment plans. It also highlights the importance of considering gender differences in clinical practice to better meet the specific needs of patients and optimize treatment outcomes.

Based on previous reports of research on biomarkers associated with LRRK2 G2019S mutations in PD, we identified a number of potential candidates.[50–54] We observed higher serum NFL at baseline in the PD + G2019S mutant group, which may be associated with a higher risk of motor or cognitive progress.[55] In addition, the ratios of some biomarkers also have potential research significance. This provides valuable insights into the biomarker profile associated with LRRK2 G2019S mutations in PD and lays the foundation for further research in this area.

The results have triggered further contemplation regarding the connection between LRRK2-G2019S and the pathobiology of PD. Numerous investigations have established a strong correlation between the LRRK2-G2019S mutation and PD, and it is considered an ideal model for studying Parkinson's disease.[56] The protein produced by LRRK2 is a prospective kinase with a central role in PD,[3] especially in specific instances of hereditary and sporadic occurrences of the ailment. This mutation is thought to have a close association with irregularities in mitochondrial dysfunction,[18] oxidative stress,[57] autophagy,[15,16] and neuroinflammation.[19] Our findings seem to substantiate the idea that individuals bearing the LRRK2-G2019S mutation may exhibit more severe symptoms earlier in their disease progression, which might be partially attributed to the worsening of the aforementioned pathological mechanisms. However, paradoxically, their condition appears to progress at a relatively moderate rate, potentially involving intricate compensatory mechanisms and cellular restoration processes.[58]

Our study's strength lies in the comprehensive analysis that combines cross-sectional and longitudinal approaches, offering a holistic view of the clinical and biological features associated with the LRRK2 G2019S mutation in PD. However, we acknowledge certain limitations. Medication effects and non-pharmacological treatments may introduce bias into our results, necessitating future refinement. Furthermore, the applicability of our findings to different populations, particularly Asians,[48] should be considered, as the LRRK2 G2019S mutation's prevalence varies by region and ethnicity. Future studies should involve larger, more diverse cohorts to validate our findings.

In conclusion, our study advances our knowledge of LRRK2-associated PD by revealing distinct clinical features, gender differences, and potential biomarkers associated with the G2019S mutation. These findings offer valuable insights into the pathogenesis and progression of LRRK2-related PD, emphasizing the need for personalized treatment approaches. Our research not only contributes to the understanding of PD genetics but also emphasizes the importance of a comprehensive approach that combines clinical, biological, and gender-specific considerations in unraveling the complexity of this disease.

AUTHOR CONTRIBUTIONS

X.S. and L.X. wrote the manuscript. K.D. and A.X. designed the research. Y.X. and Y.Y. performed the research. X.S. analyzed the data.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DATA AVAILABILITY STATEMENT

The data generated and analyzed during the current study are available in the PPMI database (https://www.ppmi-info.org/access-data-specimens/download-data).

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