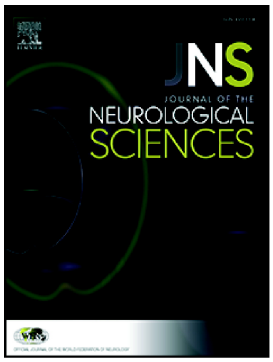

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Motor and non-motor features of Parkinson's disease in LRRK2 G2019S carriers versus matched controls

Steven A. Gunzler, MD[a]*, David E. Riley, MD[b], Shu G. Chen, PhD[c], Curtis M. Tatsuoka, PhD[d], William M. Johnson, PhD[e], John J. Mieyal, PhD[f], Ellen M. Walter, CNP[g], Christina M. Whitney, PhD[h], I. Jung Feng, PhD[i], Harry Owusu-Dapaah, MD[j], Amy L. Wilson-Delfosse, PhD[k]

[a]Parkinson's and Movement Disorders Center, Neurological Institute, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, 11100 Euclid Avenue, HAN5040, Cleveland, OH, 44106, USA, Steven.Gunzler@UHhospitals.org

[b]InMotion, 4829 Galaxy Parkway, Suite M, Warrensville Heights. Ohio, 44128, USA, Derileymd@outlook.com

[c]Department of Pathology, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA, shu.chen@case.edu

[d]Biostatistics, Neurological Institute, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, 11100 Euclid Avenue, HAN5040, Cleveland, OH, 44106, USA, curtis.tatsuoka@case.edu

[e]Department of Ophthalmology, Duke University School of Medicine, 2608 Erwin Rd, Durham, NC 27705, USA, will.m.johnson@duke.edu

[f]Department of Pharmacology, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA, jjm5@cwru.edu

[g]Parkinson's and Movement Disorders Center, Neurological Institute, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, 11100 Euclid Avenue, HAN5040, Cleveland, OH, 44106, USA, Ellen.Walter@UHhospitals.org

[h]Parkinson's and Movement Disorders Center, Neurological Institute, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine (retired), 11100 Euclid Avenue, HAN5040, Cleveland, OH, 44106, USA, twhitney02@gmail.com

[i]I Jung Feng, PhD, Epidemiology & Biostatistics, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106

[j]Department of Internal Medicine, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109, howusudapaah@metrohealth.org

[k]Department of Pharmacology, Case Western Reserve University School of Medicine, 10900 Euclid Avenue, Cleveland, OH 44106, USA, axw41@case.edu

***Corresponding Author:**
Steven A. Gunzler, MD, Parkinson's and Movement Disorders Center, Neurological Institute, University Hospitals Cleveland Medical Center and Case Western Reserve University School of Medicine, 11100 Euclid Avenue, HAN5040, Cleveland, OH, 44106, USA, Steven.Gunzler@UHhospitals.org

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Keywords: leucine-rich repeat kinase 2, autosomal dominant; Parkinson's disease; motor features; non-motor features; cognition

Abstract

Introduction: *LRRK2 G2019S mutation carriers with Parkinson's disease (PD) have been generally indistinguishable from those with idiopathic PD, with the exception of variable differences in some motor and non-motor domains, including cognition, gait, and balance. LRRK2 G2019S is among the most common genetic etiologies for PD, particularly in Ashkenazi Jewish (AJ) populations.*

Methods: *This cross-sectional data collection study sought to clarify the phenotype of LRRK2 G2019S mutation carriers with PD. Primary endpoints were the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS) and Montreal Cognitive Assessment (MoCA). Other motor and non-motor data were also assessed. The Mann-Whitney U Test was utilized to compare LRRK2 G2019S carriers with PD (LRRK2+) with non-carrier PD controls who were matched for age, gender, education, and PD duration. Survival analyses and log rank tests were utilized to compare interval from onset of PD to development of motor and non-motor complications.*

Results: *We screened 251 subjects and 231 completed the study, of whom 9 were LRRK2+, including 7 AJ subjects. 22.73% of AJ subjects with a family history of PD (FH) and 12.96% of AJ subjects without a FH were LRRK2+. There were no significant differences between the 9 LRRK2+ subjects and 19 matched PD controls in MDS-UPDRS, MoCA, or other motor and non-motor endpoints.*

Conclusion: *Prevalence of the LRRK2 G2019S mutation in AJ and non-AJ subjects in our study population in Cleveland, Ohio was comparable to other clinical studies. There were no significant motor or non-motor differences between LRRK2+ PD and matched PD controls.*

1. Introduction

The autosomal dominant G2019S mutation in the leucine-rich repeat kinase 2 (*LRRK2*) gene is among the most common genetic mutations associated with PD.[1] This mutation is responsible for 4% of familial PD and 1% of sporadic cases of PD,[2] with a higher frequency of up to 18% of PD in Ashkenazi Jews (and up to 30% of familial cases).[3]

The clinical manifestations of PD in LRRK2 mutation carriers were generally similar to those of sporadic PD,[4, 5] although some studies found a milder motor phenotype in carriers.[2, 6] Some authors found that G2019S carriers were more likely to display the postural instability-gait difficulty (PIGD) phenotype with falls.[7, 8] The International LRRK2 Consortium found a higher incidence of tremor as the presenting symptom, prevalence of dystonia, slower motor progression, and lower incidence of cognitive impairment in carriers.[2] Some authors,[9, 10] but not others,[11-14] found less cognitive impairment in G2019S carriers compared to non-carriers with PD.

This cross-sectional data collection study sought to compare motor Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS), Montreal Cognitive Assessment (MoCA), and other characteristics between LRRK2 G2019S-positive subjects and matched PD controls without the mutation recruited from an academic medical center in Cleveland, Ohio.

2. Materials and methods

2.1. Clinical Data Collection

The protocol and consent form were approved by the University Hospitals Institutional Review Board. Consecutive PD patients in an academic Parkinson's and Movement Disorders Center were offered an opportunity to participate. Ashkenazi Jewish (AJ) patients, defined as two or more AJ grandparents, were preferentially recruited. Subjects gave written informed consent. De-identified data were entered into a secure REDCap electronic data capture database hosted at Case Western Reserve University. Proper permissions were obtained for use of clinical scales.

Each subject completed a written 103-item questionnaire, with caregiver assistance when necessary. The questionnaire inquired about demographic data (including the ethnic origin of grandparents), medications, as well as motor and non-motor symptoms. The MDS-UPDRS, MoCA, Modified Hoehn & Yahr (mH&Y), Schwab & England disability scale (S&E), Non-Motor Symptom Assessment Scale (NMSS), and the Epworth Sleepiness Scale (ESS) were administered. A clinician reviewed each questionnaire with the subject, along with chart review.

2.2. Isolation of DNA from human blood

Human blood samples totaling 30cc were collected. 10 ml of red blood cell lysis buffer (0.155 M ammonium chloride, 0.01 M potassium bicarbonate, 0.00013 M EDTA) was added to 5 ml of cryogenically frozen blood and rocked for 15 minutes. The mixture was spun at 1500g, and supernatant removed. 10 ml of red cell lysis buffer was again added, rocked for 10 minutes, spun down, and supernatant removed. 5 ml of lysis buffer (10 mM Tris-HCl pH 8.0, 25 mM EDTA, 0.5% SDS) was added to the pellet and vortexed for 15 seconds. 5 ml of 5M ammonium acetate was added to the mixture and the resultant suspension was vortexed for 20 seconds, and centrifuged at 2000g for 5 minutes. The supernatant was transferred to a new tube and the procedure was repeated two more times. The final supernatant was transferred to a new tube containing 2.5 ml isopropanol, and inverted several times. The DNA/isopropanol mixture was centrifuged at 2000g for 3 minutes and the supernatant was discarded. The DNA pellet was washed with 3 ml of 70% ethanol and centrifuged at 2000g for 3 minutes. Each pellet was air-dried and DNA was resuspended in H_2O.

2.3. Identification of the LRRK2-G2019S mutation via PCR screening

Complementarity of the terminal 3' nucleotide sequence on a primer to DNA is required for PCR product amplification. Patient DNA was screened via PCR using two distinct forward primers terminating in either a guanidine or an adenosine nucleotide corresponding to the rs34637584 variant associated with the glycine to serine mutation. Patient DNA was subjected to PCR amplification using both sets of forward primers. Patients who were homozygous for the wild-type allele (guanidine) only amplified a PCR product with the "WT" primer and patients

who were heterozygotes for the mutant/wild-type alleles amplified a PCR product using both sets of primers (no homozygous mutant/mutant carriers were identified in our screen). PCR amplification was performed using GoTaq polymerase (Promega) using the following primers: Left Primer WT 5'-ATC ATT GCA AAG ATT GCT GAC TAC G- 3'; Left Primer G2019S 5'- ATC ATT GCA AAG ATT GCT GAC TAC A- 3'; Common right primer GCT TGC TTA GGT TTT GAC ACC A -3'. DNA was run on a 1% agarose gel and visualized using ethidium bromide staining. Heterozygous patients (and matching controls) were verified using Sanger sequencing.

2.4. Verification of PCR-based method via Sanger sequencing

A 991bp fragment containing the rs34637584 region was amplified from all positive samples and matching controls using GoTaq polymerase (Promega). The following primers were used to amplify the region of interest. Left 5'-TCC AAA AAT TGG GTC TTT GC-3'; Right 5'- CAG CCC CCT GTA CTC AAA CA-3'. DNA was sent to Biotic Solutions and sequenced using the following primer 5'-GGG ACA AAG TGA GCA CAG AAT-3'. Nucleotide sequence was confirmed using FintchTV (version 1.4). Sanger sequencing verified that all patients were heterozygous for the G2019S mutation. Subjects were not informed of their LRRK2 status per IRB stipulation.

2.5. Statistical Methods

We analyzed data for PD subjects who completed the questionnaire and examination, provided information about ethnicity, and had genetic testing. We calculated the prevalence of the LRRK2 G2019S mutation in AJ (defined as 2 or more AJ grandparents) and non-AJ subjects.

Utilizing the Mann-Whitney U Test, we compared baseline characteristics of PD between LRRK2 G2019S positive (LRRK2+) subjects who completed the study questionnaire and LRRK2 G2019S negative controls (LRRK2-) after matching for age, gender, duration of PD, and educational attainment. The distribution of MDS-UPDRS and MoCA (our primary endpoints), NMSS, S&E, mH&Y, and ESS scores and sub-scores were compared between LRRK2+ subjects and matched LRRK2- controls utilizing the Mann-Whitney U Test as well.

We compared the interval from onset of PD to onset of motor and non-motor complications (INT), between LRRK2+ subjects and LRRK2- controls matched for age, PD duration, education, and gender. Survival analyses were utilized to compare INT values between LRRK2+ subjects and matched LRRK2- controls, with censored values representing complications that had not yet occurred by end of observation period. We utilized Log Rank (Mantel-Cox) to compare INT between LRRK2+ and LRRK2- groups.

3. Results

251 subjects gave informed consent, of whom 242 completed the study questionnaire. 231 subjects (54 AJ and 177 non-AJ), who had complete data sets including genetic testing and ethnicity data, were included in our analyses. Baseline characteristics subdivided by LRRK2 genetic status are listed in Table 1. In the LRRK2+ group, 4 subjects initially presented with rest tremor, 4 dragged or shuffled a foot, and 1 had dyscoordination.

Seven of 54 (12.96%) AJ subjects and 2 of 177 (1.13%) non-AJ subjects were carriers of the LRRK2 G2019S genetic mutation. 5 of 22 (22.73%) AJ subjects with a family history (FH) of PD and 2 of 32 (6.25%) sporadic AJ subjects were carriers. 0 of 67 (0%) non-AJ subjects with FH of PD were carriers; thus the two non-AJ carriers represented sporadic cases of PD.

Nineteen LRRK2- subjects were matched with the 9 LRRK2+ subjects for age, gender, educational attainment, and duration of PD. Five of 19 (26.32%) LRRK2- controls were AJ with a FH of PD, compared to 5 of 9 (55.56%) LRRK2+ subjects. 2 (22.22%) LRRK2+ subjects were AJ without a FH of PD, compared to 5 (26.32%) matched controls. 0 (0%) LRRK2+ subjects were non-AJ with FH and 2 (22.22%) were non-AJ without FH, whereas 3 (15.79%) LRRK2- matched controls were non-AJ with FH and 6 (31.58%) were non-AJ without FH.

There was no significant difference in MoCA or other motor and non-motor scales and characteristics between the LRRK2+ subjects and the LRRK2- PD controls (Table 2a).

Specifically, there was no significant difference in MDS-UPDRS, mH&Y, NMSS, MoCA, S&E, ESS, levodopa equivalents, or smoking status. The percentage of subjects with self-reported motor and non-motor complications also did not differ between LRRK2+ subjects and matched PD controls (Table 2b).

33.33% (3 of 9) of LRRK2+ subjects had a history of deep brain stimulation (DBS) surgery, compared with 15.79% (3 of 19) of matched controls. Amongst the subjects with motor fluctuations, no LRRK2+ subject and 1 LRRK2- subject was in the "off" state at the time of the MDS-UPDRS. Excluding the one subject in the "off" state, mean (SD) MDS-UPDRS was 73.78 (29.02) for the 9 LRRK2+ subjects and 66.89 (27.81) for the 18 controls (p=0.668), and mean (SD) mH&Y was 3.00 (0.61) for the LRRK2+ subjects and 2.72 (0.71) for the controls (p=0.275).

To determine the latency from onset of PD to onset of various motor and non-motor complications of PD, we utilized survival analyses. Censored data points occurred when the individual motor complication had still not occurred by the time of questionnaire completion. We found no significant difference between LRRK2+ subjects and matched PD controls in interval from onset of PD to development of motor fluctuations (p= 0.897), dyskinesia (p= 0.478), memory loss (p=0.498), urinary control (p=0.402), dizziness (p=0.261), hallucinations (p=0.180), falls (p=0.407), or freezing of gait (p=0.612).

4. Discussion

There is a heterogeneity of PD clinical subtypes as well as a variety of genes that have been implicated in PD. In order to better predict future PD symptomatology as well as to tailor treatment to a particular genotype, the phenotypes of genetic PD must be better defined. This cross-sectional data collection study demonstrated no significant differences in motor and non-motor phenotype between LRRK2+ subjects and matched controls in our study population.

The prevalence of LRRK2 G2019S carrier status was 12.96% and 1.13% amongst AJ and non-AJ subjects respectively, with a prevalence of 22.73% amongst AJ subjects with a FH of PD, in this study population in Cleveland, Ohio. This represents a similar prevalence in our AJ population compared to other series of AJ subjects with PD.[2, 3] This report, to our knowledge, is the first description of the prevalence of LRRK2 carrier status amongst AJ and non-AJ subjects at a mid-western medical center in the United States.

Motor and non-motor characteristics of PD, such as gait and cognition, can be influenced by age and duration of disease. Additionally, educational attainment and gender can be potential confounders. After controlling for these variables, there was no significant difference, nor was there any trend toward a difference, in the MDS-UPDRS motor examination or MoCA, our primary endpoints.

Several authors also reported a similar cognitive profile in LRRK2 G2019S carriers compared to LRRK2 negative PD. [11-14] Although a milder cognitive decline was found in LRRK2 carriers relative to PD controls in two studies, these subjects comprised a more

heterogeneous genotype, including LRRK2 R1441G and R1441C mutations, respectively. [9, 10] Additionally, the large International LRRK2 Consortium looked at a very different cognitive endpoint (mini mental status examination ≤ 24) and did not match for level of education or other confounders. [2]

Although MDS-UPDRS motor scores and the percentage of patients with motor complications did not differ between the two groups, there was a trend toward a higher prevalence of falls in the LRRK2+ group (p=0.062). This would be consistent with some reports that G2019S carriers were more likely to display the PIGD phenotype with falls.[7, 8] Larger sample sizes are needed to further investigate these findings. A potential confounder is the higher proportion of LRRK2+ subjects who had DBS compared with matched controls, which may inflate the motor status in the LRRK2+ group.

Although this was a pilot study with a small sample size of LRRK2+ subjects, no clear differences emerged between the LRRK2+ subjects and controls, particularly between motor MDS-UPDRS and MoCA, the primary endpoints. We found a similar motor and non-motor profile, in addition to a similar sequence of motor and non-motor symptom onset, as determined by survival analyses. Larger studies will continue to be needed to better define the phenotype of LRRK2 G2019S carriers with PD.

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Table 1: Baseline characteristics subdivided by LRRK2 G2019S carrier status

	LRRK2 Positive (N=9)			**LRRK2 Negative (N=222*)**
	mean	standard deviation	mean	standard deviation
Age	77.11	6.45	68.87	11.07
Age at Onset	60.83	8.34	59.59	12.20
Duration of PD	16.28	5.52	9.27	6.34
Smoking (pack-years)[b]	11.00	13.20	9.20	19.55
Levodopa equivalents[b]	970.94	589.13	692.53	519.69
Montreal Cognitive Assessment[c]	24.33	2.65	23.96	4.35
Non-Motor Symptom Assessment Scale[a]	69.22	43.99	47.60	35.59
Epworth Sleepiness Scale[c]	11.00	5.2	8.54	5.55
MDS-UPDRS	73.78	29.02	55.95	25.96
S&E "on" or non-fluctuator (percentage)	77.78	16.41	82.16	15.45
Modified Hoehn & Yahr	3.00	0.61	2.43	0.71
	number	percentage	number	percentage
Gender female	1	11.11%	87	39.19%
Positive family history of PD	5	55.56%	85	38.29%
Motor Fluctuations	6	66.67%	118	53.15%
Dyskinesia	7	77.78%	94	42.34%
Educational attainment (graduated from):				
None	0	0.00%	3	1.35%

Grade school	0	0.00%	5	2.25%
High school	2	22.22%	87	39.19%
College	4	44.44%	64	28.83%
Graduate school	3	33.33%	63	28.38%
Number of AJ grandparents:				
4	7	77.78%	44	19.82%
3	0	0.00%	0	0.00%
2	0	0.00%	3	1.35%
1	0	0.00%	4	1.80%
0	2	22.22%	171	77.03%

PD=Parkinson's disease; MDS-UPDRS=Movement Disorder Society Unified Parkinson Disease Rating Scale;

S&E=Schwab & England; AJ=Ashkenazi Jewish; N=total number of subjects analyzed

*N=222 in the LRRK2 negative group except for [a]N=219, [b]N=220, and [c]N=221

Table 2: Comparison of (a) motor and non-motor characteristics and (b) self-reported motor and non-motor complications between LRRK2 G2019S carriers and LRRK2 G2019S negative matched PD controls

	LRRK2 Positive (N=9)*		LRRK2 Negative (N=19)*		
(a)	mean	standard deviation	mean	standard deviation	p-value[a]
MDS-UPDRS	73.78	29.02	65.84	27.41	p=0.595
MDS-UPDRS Part I	17.33	9.39	15.37	8.22	p=0.809
MDS-UPDRS Part 2	24.33	10.49	18.89	10.58	p=0.263
MDS-UPDRS Part 3	26.78	10.98	26.47	14.00	p=0.664
MDS-UPDRS Part 4	5.33	4.15	5.11	4.71	p=0.735
Modified Hoehn and Yahr	3.00	0.61	2.71	0.69	p=0.243
Non-Motor Symptom Assessment Scale (NMSS)	69.22	43.99	55.83	36.48	p=0.403
NMSS D1 Cardiovascular	3.33	3.71	1.95	3.22	p=0.530
NMSS D2 Sleep/Fatigue	14.11	8.31	14.84	7.76	p=0.962
NMSS D3 Mood/Cognition	10.56	13.79	9.89	12.84	p=1.000
NMSS D4 Perceptual Problems/Hallucinations	4.78	6.52	4.58	6.33	p=0.962
NMSS D5 Attention/Memory	7.78	6.46	9.32	9.76	p=0.962
NMSS D6 Gastrointestinal Tract	7.56	5.88	5.26	4.24	p=0.308
NMSS D7 Urinary	15.11	12.26	8.78	8.71	p=0.145
NMSS D8 Sexual Function	2.78	1.56	2.58	1.77	p=0.699
NMSS D9 Miscellaneous	3.22	1.72	2.84	2.32	p=0.438
Montreal Cognitive Assessment (MoCA)	24.33	2.65	23.63	3.47	p=0.595
MoCA Visuospatial/Executive	3.44	1.51	3.32	1.29	p=0.809
MoCA Naming	2.78	0.44	2.74	0.45	p=0.885
MoCA Attention	5.67	0.71	5.58	0.84	p=0.885
MoCA Language	2.11	0.60	2.26	0.65	p=0.595
MoCA Abstractions	1.89	0.33	1.42	0.77	p=0.172
MoCA Delayed Recall	2.44	1.33	2.32	1.64	p=0.699
MoCA Orientation	5.89	0.33	5.79	0.54	p=0.847
S&E "on" or non-fluctuator (percentage)	77.78	16.41	74.21	20.36	p=0.772
Epworth Sleepiness Scale	11.00	5.20	8.68	6.56	p=0.188
Levodopa Equivalents (mg)	970.94	589.13	805.42	665.13	p=0.223
Smoking Status (pack-years)	11.00	13.20	9.16	16.38	p=0.595
(b)	number	percentage	number	percentage	p-value[b]
Motor Fluctuations	6	66.67%	11	57.89%	p=1.000
Dyskinesia	7	77.78%	14	73.68%	p=1.000
Memory Loss	8	88.89%	12	63.16%	p=0.214
Urinary Control Issues	8	88.89%	14	73.68%	p=0.630
Dizziness	5	55.56%	11	57.89%	p=1.000
Hallucinations	5	55.56%	11	57.89%	p=1.000
Falls	9	100.00%	12	63.16%	p=0.062
Freezing of Gait	8	88.89%	11	57.89%	p=0.414

* matched for age, educational attainment, duration of Parkinson's disease, and gender

[a] Two-Sided Independent Samples Mann-Whitney U Test

[b] Two-sided Fisher's Exact Test

PD=Parkinson's disease; MDS-UPDRS=Movement Disorder Society Unified Parkinson Disease Rating Scale; S&E=Schwab & England; AJ=Ashkenazi Jewish

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Highlights:

- LRRK2 G2019S is a common genetic mutation in familial Parkinson's disease (PD).
- We sought to determine phenotype and prevalence of LRRK2 G2019S carriers with PD.
- We determined PD phenotype and LRRK2 G2019S carrier status in 231 subjects.
- 13% of Ashkenazi Jewish (AJ) and 1% of non-AJ subjects were LRRK2 G2019S carriers.
- PD phenotype was similar between LRRK2 G2019S carriers and matched PD controls.