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Clinical Expression of LRRK2 G2019S Mutations in the Elderly

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Abstract

Mutations in the leucine-rich repeat kinase 2 gene (*LRRK2*, PARK8) are the most commonly identified monogenic etiology of Parkinson disease (PD). Over-represented in the Ashkenazi Jewish (AJ) population, these mutations are transmitted in an autosomal dominant manner with age-dependent reduced penetrance. The natural history and penetrance of these mutations in the elderly is controversial and inadequately studied. We conducted a nested cohort study in a community-based aging study (the Einstein Aging Study, EAS). Six elderly, initially non-manifesting carriers (NMC) of the *LRKK2* G2019S mutation were identified (average age 82.1±7.0, range 72.7-90.8), and five had available longitudinal data. We matched 5 non-carrier controls to each NMC and followed them for an average of 4.7 years with annual cognitive and motor examinations. PD was identified in one NMC at age 95 and in no control subjects. The remaining carriers did not differ from controls on motor scores at baseline or follow-up. The baseline Unified Parkinson's Disease Rating Scale motor subscore (UPDRS-III) in cases was 6.2±6.9 (range 1-19) and in controls was 4.5±6.6 (1-30), p=0.6; the mean difference in UPDRS-III slopes over time between cases and controls was 0.1±1.3 and was not statistically significant. Our data, while limited by a small sample size, show that in *LRKK2* G2019S mutation carriers, phenoconversion to PD can occur late in life. However, most NMC have motor decline which indistinguishable from their age mates, suggesting that the larger subset of elderly non-manifesting carriers is not on the motor trajectory to disease.

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Documentation of Author Roles

1. Research project: A. Conception, B. Organization, C. Execution
2. Statistical analysis: A. Design, B. Execution, C. Review and Critique
3. Manuscript: A. Writing of first and subsequent drafts, B. Review and Critique M. San Luciano: 1A, 1B, 1C, 2A, 2B, 3A; R. Lipton: 1A, 1C, 2A, 2C, 3B; C. Wang: 2A, 2B, 2C; M. Katz: 1B, 1C, 2C, 3B; M. Zimmerman: 1C, 3B; A. Sanders: 1C, 3B; L. Ozelius: 1C, 3B; S. Bressman: 1A, 2C, 3B; R. Saunders-Pullman: 1A, 1B, 1C, 2A, 2C, 3B.

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Keywords

LRRK2; Parkinson's disease; parkinsonism; non-manifesting carriers; penetrance; cognition; clinical

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease with an overall prevalence of approximately 1.8% over the age of 65 (1,2). While the cause of PD is usually unknown, mutations in the leucine-rich repeat kinase 2 gene (3,4) (*LRRK2*, PARK8) are the most frequently identified monogenic cause of PD. A glycine to serine substitution located in the highly conserved kinase region of exon 41 (G2019S) is responsible for approximately 4% of familial and with 1% of apparently sporadic PD (5,6) worldwide. In Ashkenazi Jews (AJ) and North African Arabs, the mutation is overrepresented (7-13) due to a common founder mutation (14-16).

While an autosomal dominant mode of transmission is accepted, the lifetime penetrance of *LRRK2* mutations is debated, with estimates ranging from 17% to 100% (7-9,17). The broad estimates may be due to methodological differences including subject ascertainment and diagnostic criteria, especially in the very elderly, where parkinsonism needs to be distinguished from normal motor aging.

The natural history of clinical expression in elderly gene carriers without diagnosed PD (non-manifesting carriers, NMC) has not been well studied. We present cross-sectional and longitudinal data on motor and cognitive features in *LRRK2* G2019S NMC and compare their motoric progression to age and gender matched subjects.

Methods

Subjects were ascertained from the cohort individuals followed annually as part of the longitudinal Einstein Aging Study (EAS) from 1993 to present. Recruitment and examination methods have been previously described (18). We first sought to identify EAS subjects who had phlebotomy for genetic studies, were screened for the *LRRK2* G2019S mutation, and had complete neurological and neuropsychological examination. We then compared each mutation positive subjects without PD (non-manifesting carriers, NMC) to five mutation negative subjects without PD matched for age (± 5 years), gender and year of study recruitment (±1 year). The matches were randomly selected from the EAS and at baseline did not have dementia or history of stroke or neuroleptic use.

Yearly neurological examinations conducted by physicians included, but were not limited to, the motor section of the Unified Parkinson's Disease Rating Scale (19) (UPDRS-III) and the Clinical Dementia Rating Scale (20,21) (CDR). History of prior diagnosis of PD and treatment with parkinsonian medications and dopamine blockers or depleters was queried, and parkinsonian gait and features were rated by the examiner based on history and examination. Diagnosis of parkinsonism was confirmed using research criteria (22,23). Dementia diagnosis was assigned at consensus case conferences using information from the neuropsychological test battery, the neurological exam and medical and social history data using the Diagnostic and Statistical Manual of Mental Disorders fourth edition criteria (24).

An extensive neuropsychological test battery validated in our and other aging populations (25) was also administered. This battery, detailed elsewhere (25) included the Trail Making

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Test (26,27) (TMT). The TMT Part B (Trails B) was used as a test of motor speed and visual attention (26,27).

Informed consent was obtained from all subjects for participation in the EAS; the study was approved by the Committee on Clinical Investigations at The Albert Einstein College of Medicine and was conducted in accordance with the Declaration of Helsinki. DNA was extracted from white blood cells using QIAamp DNA Blood Maxi Kit according to manufacturer's instructions (Qiagen, Valencia, CA). The G2019S mutation in *LRRK2* corresponds to a G6055A SNP in exon 41 and was genotyped by pyrosequencing using methods and primers described previously (8).

For statistical data analysis, SAS 9.1 (SAS Institute Inc., Cary, N.C) and STATA10 (STATA Corp., College Station, TX) were used. Non-parametric tests were employed when variables were not normally distributed. Inverse transformation was used for Trails A and B time to eliminate severe skewness and was interpreted as Trails A and B speed. To compare the longitudinal UPDRS-III scores and Trails speed between the matched *LRRK2* G2019S mutation carriers and controls, the slope over time in years was calculated for each subject and the average slope among controls in each matched set was obtained. The difference in slopes between each case and the mean in the control group was then calculated for each matched set and evaluated using a matched-pair t-test.

Results

A total of 791 subjects were screened for mutations, including 355 AJ individuals. 192 of the AJ subjects were previously reported (28). Twelve AJ subjects had definite parkinsonism (3.3%) (Table 1). Heterozygous *LRRK2* G2019S mutations were identified in 7 AJ individuals (2.1% carrier frequency among AJs) and at baseline none of them had definite parkinsonism. One of the mutation carriers was deceased shortly after intake, therefore only six of the seven mutation carriers had complete follow-up information.

Baseline characteristics are summarized in Table 2. The G2019S mutation carriers were not different from the overall matched control group except for Trails B speed, where cases had slightly shorter times (faster speed) than the control group.

The performance in UPDRS among the overall control group declined (score increased) over time with an average slope of 0.7 ± 0.5 points per year (Table 3). Among the *LRRK2* mutation carriers, UPDRS scores increased slightly faster (difference in slope of 0.1 ± 1.3 points per year, 95%CI: -1.2, 1.5) but the difference was not statistically significant. The motor slope for Subject 2, who at the end of the follow-up period met criteria for PD, was 2.8 UPDRS points per year, compared to a mean of 0.5 points per year among the other mutation positive subjects.

Trails B speed did not decline yearly among the control group. While the rate of decline in Trails B speed was faster for the *LRRK2* mutation carriers, the difference was not statistically significant (difference in slopes= -0.8 ± 0.8, 95%CI: -1.8, 0.2). The decline slope in Trails B speed for Subject 2 was -1.7 compared to an average slope of 0.1 in the other cases. Similar results were obtained for Trails A (Table 4). Graphic representation of the progression of UPDRS-III scores for each subject compared to their controls as well as to the overall control group is depicted in Figure 1.

None of the mutation carriers or controls developed dementia by the end of the follow up period.

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Clinical description

Only subject 2 developed PD by research criteria during follow-up. She is a 95 year-old woman, previously described at age 91 (28), when she was living independently, had mild slowness of gait, kyphosis and limited mobility of her leg which was attributed to a mild peripheral neuropathy, knee pain and spine osteoarthritis. At her last exam at age 95, she remained independent in her activities of daily living and lived alone. She had definite bradykinesia in her arms and legs with decrementing movement amplitude and occasional movement arrests on finger taps. She had mild rigidity in neck and both arms, and needed to push herself out of a chair to stand. Her gait was markedly slow with decreased right arm swing and shortened stride length. She recovered unaided from the pull test in two steps. Despite the lack of rest tremor, she met UK Brain Bank clinical diagnostic criteria for PD (22).

Discussion

We identified and followed a cohort of very old carriers of the common G2019S *LRRK2* mutation by screening a systematically recruited community based sample. Of our 5 *LRKK2* mutation carriers free of PD at baseline, only one developed PD. She showed gradual worsening of UPDRS-III scores suggesting progressive motor worsening during the preclinical onset of PD. For the other participants, mild motor features and change in mild motor features were similar for those without the *LRKK2* mutation.

All subjects had a mild increase in their UPDRS-III ratings over time, whether or not they carried the *LRKK2* mutation: this supports the known progression of mild parkinsonian features with aging (29); it also is consistent with reduced penetrance of PD in elderly carriers of the *LRKK2* mutation. The slope of progression of motor features was similar between mutation carriers and controls for all except Subject 2, whose steeper progression led to PD at last follow-up. That is, most of the *LRRK2* non-manifesting mutation carriers did not show evidence of accelerated motor decline. Our mutation carriers' ages at last follow-up ranged from 77 to 95 years. Several individuals with age of onset of *LRRK2* PD in their early to mid-eighties have been reported (5,7,30-32) including several with onset after age 90 (5,33). As Subject 2 did not meet criteria for PD until age 95, it is possible then that our carriers may still develop PD in the upcoming years. As a pre-clinical period of PD has been posited (34), and Subject 2, unlike the other carriers, had a steep increase in her motor scores starting five years before she met PD criteria that differentiated her curve from her matched controls, the change in UPDRS is in excess of normal motor aging.

Consistent with the known prevalence of approximately ~14% of *LRRK2* mutations among all Ashkenazi Jewish individuals with PD (2), in the 355 AJ subjects screened for the G2019S mutation, seven had idiopathic PD but none of them were carriers. Therefore even though mutations in the *LRRK2* gene are the most common genetic determinant of PD identified to date among the Ashkenazim (6), the etiology of PD in most cases remains largely unexplained.

A strength of our study is that our sample was derived from a community based cohort, and thus we may have selected a more benign group, as our carriers were not ascertained based on the presence of PD or family history of PD. While this would not detract from our finding of incomplete penetrance, our sample cannot be used to estimate overall penetrance in the elderly, as individuals with PD might be more likely to be living in care facilities than at home. Finally, because this elderly group has survived for the longest period without PD, they constitute a unique cohort possibly enriched for increased protective or a lower burden of deleterious factors.

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The motoric progression of the carrier who manifested PD suggests that there is a period of motoric worsening which precedes clinical *LRRK2* PD and can be distinguished from normal aging. Further prospective evaluation will allow us to determine whether similar motor slopes are observed prior to the development of PD in other carriers.

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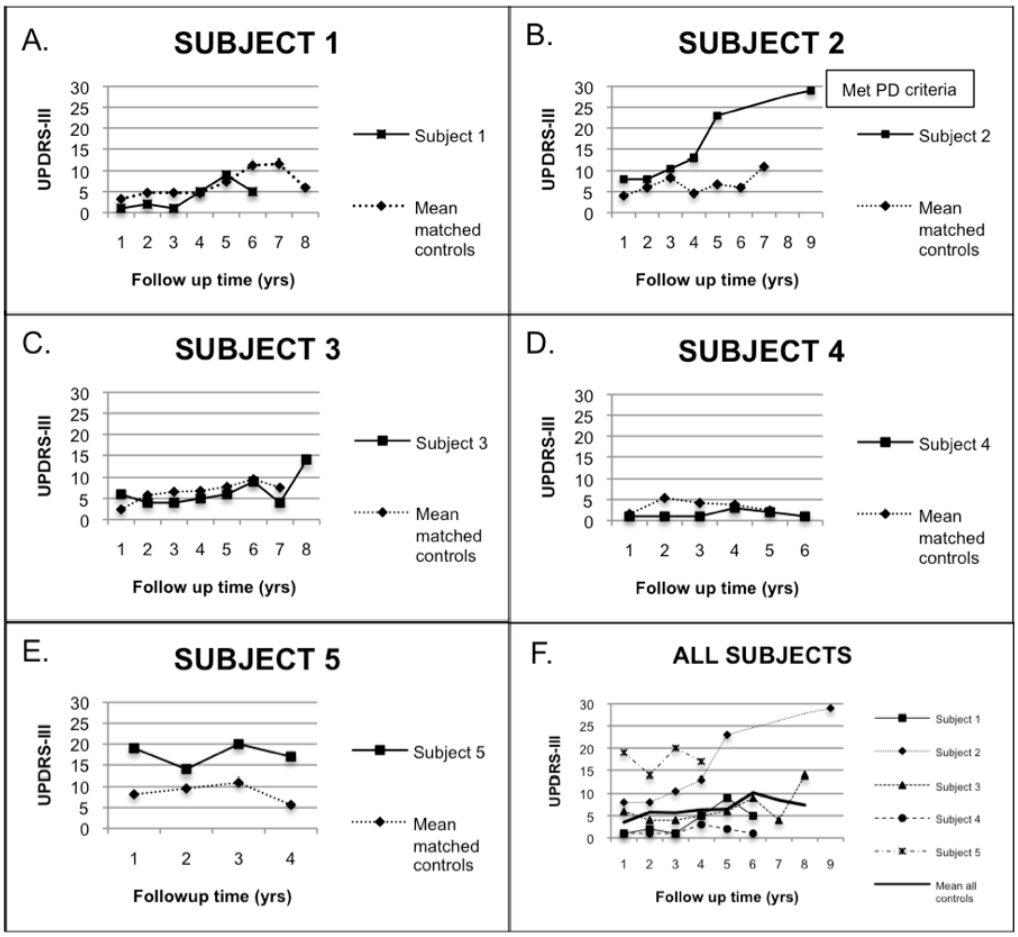

Figure 1.

Longitudinal UPDRS-III ratings in *LRRK2* G2019S carriers and controls

Figures A-E are graphic representations of UPDRS-III scores over time of the different subjects compared to the mean of their matched control set. Subject 2 had missing UPDRS-III points from years 6-8. In Figure F, mean UPDRS-III scores are presented for all subjects and controls using the same Y-axis scale.

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TABLE 1

Characteristics of the screening population

	N	Female (%, n)	Age (Years±SD)	Parkinsonism	Type of parkinsonism
AJ*	355	58.9% (209)	83.2±5.7	12/355	7 IPD** 1 drug-induced parkinsonism 2 AD-related parkinsonism*** 1 diffuse Lewy body disease 1 mild axial parkinsonism at age 100
Carriers	7	85.7% (6)	87.7±6.9	0/7	
Non carriers	348	58.3% (203)	83.1±5.7	12/348	
Non AJ	436	63.8% (278)	81.4±5.5	15/436	9 IPD** 1 drug-induced parkinsonism 2 AD-related parkinsonism*** 2 vascular parkinsonism 1 NPH****
Carriers	0				
Non carriers	436	63.8% (278)	81.4±5.5	15/436	

* AJ: Ashkenazi Jews

** IPD: Idiopathic Parkinson's disease

*** AD-related parkinsonism: Alzheimer's disease related parkinsonism

**** NPH: Normal pressure hydrocephalus

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TABLE 2

Baseline characteristics of *LRRK2* mutation carriers and controls

	***LRRK2* carriers (n=6)**	**Control subjects (n=30)**	**All subjects (n=36)**
UPDRS-III*	6.2 ± 6.9 (1-19)	4.5 ± 6.6 (1-30)	4.8 ± 6.6 (1-30)
Trails B speed**	42.0 ± 8.9	31.0 ± 3.1	36.0 ± 8.4
CDR*	0.1 ± 0.2	0.1 ± 0.2	0.1 ± 0.2
BIMC*	0.8 ± 0.7	2.3 ± 2.4	2.1 ± 2.3
FCSRT* (free recall)	31.8 ± 3.2	31.6 ± 5.4	31.6 ± 5.1

LRRK2: Leucine Rich Repeat Kinase 2; UPDRS-III: Unified Parkinson's Disease Rating Scale, motor subscale, mean±SD (range); CDR: Clinical Dementia Rating Scale, mean±SD; BIMC: Blessed Information Memory Concentration test, mean±SD; FCSRT: Free and Cued Selective Reminding test, mean±SD.

* p>0.05;

** p=0.02

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TABLE 3

Clinical characteristics and UPDRS-III total and subscores of *LRRK2* G2019S carriers and matched controls*

Subject	Sex (n)	Family history**	Follow up time (yrs)	UPDRS-III at First Exam						UPDRS-III at Last Exam						Meets PD criteria
				Age (yrs)	Total score	RT	R	B	P/G	Age (yrs)	Total score	RT	R	B	P/G	
1	M	+	5.67	78	1	0	0	0	1	84	5	0	0	0	5	No
Controls-1	M(5)		6.1±0.9	76.9±2.9	3.2 (2-6)	0	0	0.4 (0,2)	2.5 (2,4)	82.9±3.3	8 (2,16)	0	0.2 (0,1)	3.4 (0,8)	4 (2,8)	No
2	F	+	8.28	86	8	0	0	0	7	95	29	0	5	16	7	Yes
Controls-2	F(5)		5.4±1.8	84.2±1.1	5	0	0	2	2 (1,3)	89.6±1.0	7.5 (1,11)	0	0	5.2 (0,10)	3.25 (1,8)	No
3	F	+	7.33	81	6	0	0	2	4	88	14	0	0	6	6	No
Controls-3	F(5)		7.0±0.2	81.1±3.0	2.4 (1,6)	0	0	0	2.4 (1,6)	88.1±3.0	7.2 (3,18)	0.2 (0,1)	0	4.4 (0,9)	2.4 (0,9)	No
4	F	-	4.31	72	1	0	0	0	1	77	1	0	0	1	0	No
Controls-4	F(5)		4.0±0.1	72.3±2.7	1.6 (1,3)	0	0	0	1.2 (1,2)	76.3±2.6	2.4 (0,7)	0	0	0.6 (0,2)	1 (0,5)	No
5	F	-	3.9	90	19	0	2	11	6	94	25	0	0	15	10	No
Controls-5	F(5)		2.6±0.5	86.9±1.4	8.2 (2,30)	0	0.6 (0,2)	3.6 (0,16)	4 (1,12)	89.6±1.7	12 (1,27)	0	0	5.8 (0,12)	5.8 (1,15)	No
6	F	-	0	85	2	0	0	1	1	-	-	-	-	-	-	No
Controls-6	F(5)		2.7±0.5	83.3±2.7	6.6 (1,20)	0	0	3.6 (0,14)	1.8 (1,4)	86.1±2.3	9.6 (5,15)	0	1.2 (0,4)	4.4 (0,8)	3.6 (1,7)	No

*UPDRS-III: Unified Parkinson's Disease Rating Scale, Motor Subscale; RT: Rest tremor component of UPDRS-III; R: Rigidity component of UPDRS-III; B: bradykinesia component of UPDRS-III, not including speech and facial expression; P/G: postural changes and gait component of UPDRS-III. Years of follow up and age are expressed in mean years ± S.D. UPDRS and subscores are expressed in mean points and range.

**Subjects 1-2 had a family history of Parkinson's disease in first-degree relatives. Subject 6's mother carried a diagnosis of Pick's disease.

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TABLE 4

UPDRS-III and Trails A and B difference in baseline and slopes between *LRRK2* G2019S mutation carriers and controls*

	Mean difference ±SD	95% CI	Minimum	Maximum
UPDRS-III Baseline	0.7 ± 5.4	-4.1, 7.4	-4.6	10.8
UPDRS-III Slopes	0.1 ± 1.3	-1.2, 1.5	-1.6	2.2
Trails A speed Baseline	-2.8 ± 7.8	-11, 5.4	-14.8	7.3
Trails A speed Slopes	-0.3 ± 5.2	-5.8, 5.2	-9.8	5.6
Trails B speed Baseline	10.4 ± 8.3	0.04, 20.7	-1.8	16.8
Trails B speed Slopes	-0.8 ± 0.8	-1.8, 0.2	-1.9	0.2

* Free recall (31.8±3.2 for cases and 31.6±5.4 for controls) and Blessed scores (0.8±0.7 for cases and 2.3±2.4 for controls) at baseline and at the end of the follow up period (31.3±4.1 for cases and 32.6±6.8 for controls; 2.17±1.5 for cases and 2.1±2.7 for controls) as well as the calculated progression slopes for both were not significantly different between cases and controls.