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LRRK2 G2019S Mutations are associated with an increased cancer risk in Parkinson Disease

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Abstract

Leucine rich repeat kinase (*LRRK2*) G2019S mutations are presumed to cause PD through a toxic gain of function of the protein kinase. Small molecule kinase inhibitors have been developed for the treatment of certain cancers, and some antioncogenic agents such as sunitinib, may non-specifically inhibit *LRRK2*. Few studies, however, have assessed cancer risk in *LRRK2* mutation carriers. To explore this risk, we evaluated records of Ashkenazi Jewish (AJ) PD patients participating in genetic research. Charts were reviewed for 163 unrelated AJ PD patients, 31 of whom harbored the G2019S mutation. History of cancer was queried at baseline intake using a form reviewing medical conditions, and charts were reviewed for all follow-up visits. 9/31 *LRRK2* G2019S mutation carriers had non-skin cancers, whereas 15/132 without mutations had non-skin cancers, representing an almost three-fold increased risk in this group (HR 2.9, 95% CI 1.3-6.6).

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Age at first non-skin cancer was younger in the *LRRK2* carriers (56.0 years) than the non-carriers (62.0 years), but was not significant. 67% of the *LRRK2* carriers had their cancer before the onset of PD, whereas only 40% of non-carriers developed their first non-skin cancer before onset of PD. While further evaluation is warranted, our findings indicate an increased risk of non-skin cancers in *LRRK2* G2019S mutation carriers, which may be related to toxic gain of function of mutated *LRRK2*.

Keywords

genetics; Parkinson Disease; *LRRK2*; cancer; renal cancer

Introduction

Mutations in the *LRRK2* gene are the most frequent monogenic cause of Parkinson Disease (PD) (1-6). While the pathophysiologic mechanism of *LRRK2* mutations is unknown, in vitro studies have shown that mutations confer increased *LRRK2* kinase activity (7-16), and cellular models overexpressing wild type and mutant *LRRK2* demonstrate aggregation and cellular toxicity (17). This toxic gain-of-function, however, has not yet been demonstrated in vivo (18).

Small molecule kinase inhibitors have already been developed for the treatment of certain cancers, and it is hoped that these drugs may also play a role in modulating *LRRK2* related PD (19). To date, few studies have assessed cancer risk in *LRRK2* mutation carriers. In one report, the *LRRK2* G2019S mutation was not associated with melanoma (20), a cancer type consistently associated with PD (21-24). However, clustering of non-skin cancers among gene carriers was noted in the large Western Nebraska kindred with the R1441C *LRRK2* mutation (25). To further explore the risk of cancer in *LRRK2* mutation carriers, we evaluated records of Ashkenazi Jewish (AJ) PD patients participating in research studies of the *LRRK2* G2019S mutation, a mutation especially common in this population (5,26).

Methods

Records were reviewed for subjects with PD who were of AJ descent and participated in an ongoing genetic research study of *LRRK2*-related PD at the tertiary Movement Disorder Center at Beth Israel Medical Center in New York City (5), and who were evaluated in the last eighteen months. This study was approved by the Institutional Review Board. *LRRK2* G2019S mutation status was determined as previously described (5). Ancestry was self-reported. Movement disorder specialists performed clinical assessments including The Unified Parkinson's Disease Rating Scale (UPDRS) (27), and all subjects met strict diagnostic criteria for PD (28). History of cancer was queried at baseline intake using a form reviewing medical conditions, and confirmed by the examining physician at first visit. Charts were reviewed for all follow-up visits to determine subsequent cancers. Cancer type was noted, and cancers were coded as non-skin cancers or melanoma. Attempts were made to obtain records from the treating oncologist, surgeon and/or internist when a melanoma or non-skin cancer was noted at intake or at follow-up. UPDRS part III motor scores and medication doses were extracted from the most recent visit. Smoking history was categorized by ever/never smoker, and years smoked. T-tests and Mann-Whitney, chi-square and Fisher's exact tests were used for univariate analyses of demographic and disease features, odds ratio were determined using logistic regression models and Cox proportional hazards models were used to assess outcome of cancer, censoring at age of first non-skin cancer or age at last exam cancer-free. Graphical and goodness-of-fit approaches were used to evaluate the proportional hazards assumption. STATA10 software (STATA Corp College

Station, TX) was used for all statistical analyses. As melanoma is believed to have a separate genetic basis from other cancers in PD (29,37), and was not previously associated with *LRRK2* (20), we focused primarily on non-skin cancer.

Results

Charts were reviewed for 163 unrelated PD patients, 31 of whom harbored the G2019S mutation. Clinical features are summarized in Table 1. *LRRK2* G2019S mutation carriers did not differ from non-mutation carriers in their median age at last exam (68.7 years vs. 71.2 years) and median years of follow-up of PD at Beth Israel (4.7 years vs. 4.5 years), however, as expected, there was a trend for the *LRRK2* mutation carriers to have an earlier age of onset (57.0 vs. 59.5). *LRRK2* mutation carriers were more likely to be female (55% vs. 44%), but this was not significantly different. *LRRK2* mutation carriers did not differ in the percentage taking levo-dopa (L-dopa) at last visit (71% vs. 79%) or median dose (450 vs. 450 mg equivalent of L-dopa), however there was a trend for the median motor UPDRS to be lower in the *LRRK2* group (12.5 vs. 16.0).

There was an almost three-fold increased risk of non-skin cancers in *LRRK2* mutation carriers when age at first cancer or age at last exam cancer free was included in the model (HR 2.9, 95% CI 1.3-6.6) (Table 2). Neither history of smoking, years smoked, nor gender was independently associated with development of non-skin cancer. When both gender, and history of smoking were included in the model, the magnitude of the risk of non-skin cancer in the *LRRK2* group compared to non-mutation carriers did not change (OR 2.8, 95% CI 1.2-6.4).

Within the *LRRK2* group (9 individuals with cancer) (Table 3), there were three prostate adenocarcinomas, two renal cancers, three breast cancers, two lung cancers and one hematologic cancer (acute myelogenous leukemia). Two of the *LRRK2* mutation subjects with non-skin cancer also had non-recurrent non-metastatic melanoma. Three of nine individuals had two or more cancers. Among the non-mutation group (15 individuals with non-skin cancer), there were five prostate adenocarcinomas, seven breast cancers, two lung cancers, two lymphomas, and one ovarian cancer. Seven patients in the non-mutation group had non-recurrent non-metastatic melanomas. Among those with multiple malignancies, only the primaries are reported (Table 3). Two *LRRK2* individuals who had a history of smoking, and one non-mutation carrier who smoked developed smoking related cancers; from the cancers reported, lung, kidney and acute myelogenous leukemia are associated with smoking (30).

The median age at first non-skin cancer was younger in the *LRRK2* carriers (56.0 years) than the non-carriers (62.0 years), but this was not significantly different. Of note, 66.7% of the *LRRK2* carriers had their cancer before the onset of PD, whereas only 40.0 % of non-carriers developed their first non-skin cancer before onset of PD, despite earlier age of onset of PD among *LRRK2* carriers.

Discussion

Our findings indicate an increased risk of non-skin cancers in *LRRK2* G2019S mutation carriers. The *LRRK2* protein is a large GTP-regulated serine/threonine kinase with several protein-protein interaction domains (2,3,31,32, reviewed in 16); it is expressed in the striatum, cortex and hippocampus but also systemically, including adult human kidney (33). Although its normal function and pathogenic mechanisms remain to be fully elucidated, *LRRK2* mutations are believed to result in a toxic gain of function in kinase activity (7,11,13,17). Support for this proposed disease mechanism is strongest for the G2019S

mutation (31). The highly conserved 2019 glycine residue marks the start of a conformationally flexible activation loop important for control of kinase activity; it is thought that the serine substitution results in less flexibility, locking the kinase into a more active conformation (34). This explanation is supported by somatic cancer mutation studies, which show glycine to serine changes in kinases where increased activity is thought to underlie increased cell growth (35). Not surprisingly, kinase inhibitors, developed as one of the leading treatments for certain types of soft tissue malignancies, have been suggested as potential disease modifying agents for *LRRK2* associated PD (36). Sunitinib, used in the treatment of renal cell cancer is a protein kinase inhibitor that is a non-selective *LRRK2* inhibitor (19). This is of particular interest in that the only cases of renal cancer were in *LRRK2* subjects. However, the relation to *LRRK2* remains speculative, as no confirmed in vivo substrate is known.

While we did not note the increase in colon cancers reported in the Western Nebraska family, we noted both common (breast, prostate) and less common cancers (renal, non-smoking related lung CA) in our *LRRK2* patients. This is also consistent with the findings in the Western Nebraska kindred (25).

As the hazards ratio remained similar when we included ever smoking in the model, we do not believe that the excess non-skin cancer observed in the mutation carriers is attributable to smoking. However, we cannot fully exclude a smoking effect in this small sample, and the relative contribution of smoking should be addressed in greater detail in future studies.

We do not believe there is surveillance bias in our sample, as *LRRK2* and non-*LRRK2* groups were followed for similar periods of time, and *LRRK2* status was not known to the examiners or the patients for all study subjects at initial intake, and for most of the study subjects at follow-up exam. This is of particular importance as six of eight *LRRK2* carriers had cancers diagnosed prior to their first visit. Because we only screened for the G2019S mutation, it is possible that control individuals had undetected R1441C or other *LRRK2* mutations; however, these are not commonly reported in Ashkenazi PD cases. We cannot exclude survival bias in our cohort, as we chose to focus on individuals seen within the last 18 months to ensure systematic evaluation. It will be important to follow a cohort of AJ PD prospectively with cancer surveys to determine whether there is a survival difference, and if *LRRK2* related cancers are more likely to go into remission.

While our study is small relative to epidemiologic studies, it is unique in the large number of unrelated *LRRK2* PD cases studied. Therefore systematic assessment of cancer in a larger PD sample, including a greater number of mutation carriers and a non-PD control group is warranted. Inclusion of a non-PD control group will allow determination of whether the rate of cancers in *LRRK2* mutation carriers is increased compared to individuals without PD. Not only will further study allow testing of the overall association, but it will also provide additional insight into the types of malignancies that are increased in *LRRK2* carriers. Moreover, it will be important to assess cancer risk in populations with different *LRRK2* mutation types; some but not all mutations appear to effect kinase activity (7,11,13,14,38) and thus differences in cancer risk among *LRRK2* genotypes may illuminate mechanisms and potential treatments for both *LRRK2* associated PD and cancer.

We plan to extend this study to G2019S carriers who have not manifested PD to confirm that the cancer risk is segregating with genotype and also to better establish the temporal relationship of cancer to neurological pathology. In the Western Nebraska kindred three of four mutation positive family members with colon cancer did not have diagnosed PD, suggesting that cancer is a gene effect; this is supported by our data showing that 75% of the

cancers in *LRRK2* carriers occurred prior to the onset of PD. However we cannot exclude that cancers emerged during a pre-diagnosis period when PD was developing.

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Table 1
Clinical Features of *LRRK2* Mutation and Non-*LRRK2* Mutation PD

	All PD N= 163	<i>LRRK2</i> Mutation N=31	Non- <i>LRRK2</i> Mutation N=132	p-value (<i>LRRK2</i> vs. non- <i>LRRK2</i>)
Age Exam, years *	70.2 (62.6, 78.8)	68.7 (63.5, 76.3)	71.2 (62.5, 79.3)	p=0.55
Women (%)	75 (46%)	17 (55%)	58 (44%)	p=0.31
History of smoking (ever/never)	68 (41.2%)	15 (48.4%)	53 (40.1%)	p=0.42
Age Onset PD, years	59 (51,69)	57 (44,67)	59.5 (52,69)	p=0.10
Disease duration, years	8.7 (5.7,11.3)	8.7 (6.3, 15.8)	8.7 (5.7, 11.9)	p=0.28
Follow-up, years	4.6 (2.3, 7.5)	4.7 (2.5, 9.5)	4.5 (2.3, 7.4)	p=0.47
UPDRS, Part III	15.0 (9.5, 24)	12.5 (9, 18.5)	16.0 (10.0, 24.0)	p=0.19
Current L-dopa use (%)	126 (77.3%)	22 (70.9%)	104 (78.9%)	p=0.35
Dose l-dopa, mg equivalent (range)	450 (300,600)	450 (350,500)	450 (300,725)	p=0.64

*
 (median, interquartile range, quartile 1, quartile 3), Mann Whitney p-value

Table 2
Cancer in LRRK2 mutation and Non-LRRK2 mutation PD Subjects

	All PD (n=163)	<i>LRRK2</i> mutation PD (n=31)	Non- <i>LRRK2</i> Mutation PD (n=132)	<i>LRRK2</i> mutations vs. Non- <i>LRRK2</i>
Non-skin cancer (%)	24 (14.7%)	9 (29.0%)	15 (11.4%)	*HR: 2.9 (1.3-6.6)
Age onset first non- skin cancer, years **	60.5 (56, 67)	56.0 (54, 68)	62.0 (57, 66)	***p=0.5
Cancer before PD (%)	14 (8.6%)	6 (66.7%)	8 (40.0%)	****OR: 3.7 (1.2-11.7)

* Cox proportional hazards model, Hazards Ratio, 95% CI; adjusting for smoking: HR 2.8 (1.2-6.5); adjusting for smoking and gender HR 2.8 (1.2-6.4)

** median (interquartile range)

*** Mann-Whitney p-value

**** Logistic regression model, Odds Ratio, 95% CI

Table 3
Cancer types in LRRK2 mutation and non-LRRK2 mutation PD

LRRK2 (n=9)					Non-LRRK2 (n=15)				
Patient	Sex	Cancer Type	Patient	Sex	Cancer Type	Patient	Sex	Cancer Type	Patient
Renal (n=2)					Renal (n=0)				
1	M	Renal cell carcinoma, clear cell							
2	M *	Renal cell carcinoma, clear cell *							
Breast (n=3)					Breast (n=6)				
3	F	Breast ductal carcinoma	10	F *	Breast, tubular carcinoma				
4	F	Breast lobular carcinoma	11	F	Breast, infiltrating ductal carcinoma				
5	F *	Breast infiltrating ductal carcinoma	12	F *	Breast, unspecified				
			13	F	Breast, invasive mammary carcinoma				
			14	F *	Breast, unspecified				
			15	F *	Breast, unspecified				
Lung (n=2)					Lung (n=2)				
2	M *	Lung adenocarcinoma *	10	F *	Lung adenocarcinoma *				
3	F	Lung unspecified	16	M	Lung adenocarcinoma				
Prostate (n=3)					Prostate (n=5)				
6	M *	Prostate adenocarcinoma	17	M *	Prostate adenocarcinoma				
7	M	Prostate adenocarcinoma	18	M *	Prostate adenocarcinoma				
8	M	Prostate adenocarcinoma	19	M	Prostate adenocarcinoma				
			20	M	Prostate adenocarcinoma				
			21	M	Prostate adenocarcinoma				
Hematological (n=1)					Hematological (n=2)				
9	F *	Acute myelogenous leukemia *	22	F *	Lymphoma (Hodgkin's)				
			23	M *	Lymphoma (Non-Hodgkin's)				

<i>LRRK2</i> (n=9)			Non- <i>LRRK2</i> (n=15)		
Patient	Sex	Cancer Type	Patient	Sex	Cancer Type
Reproductive (n=0)			Reproductive (n=1)		
			24	F *	Ovarian, papillary serous cystadenocarcinoma

* designates ever smoker