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Evidence for increased completed suicide in first-degree relatives of *LRRK2* G2019S mutation Parkinson's disease

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INTRODUCTION

Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene are an important monogenic cause of Parkinson's disease (PD). Reported non-motor features of *LRRK2* PD include depression, anxiety and bipolar disorder,[1] but suicide has not been systematically

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investigated. As part of our *LRRK2* Ashkenazi Jewish Consortium study we assessed the history of death by suicide in probands and first-degree relatives with and without *LRRK2* G2019S mutations.

METHODS

The sample comprised participants from the Ashkenazi Jewish *LRRK2* Consortium study sites in Tel Aviv (Tel Aviv Medical Center) and New York (Columbia University Irving Medical Center and Mount Sinai Beth Israel).[2] PD probands were screened for the *LRRK2* G2019S mutation.[3] Genetic status of the first-degree relatives was not known. Questionnaire and pedigree information was systematically collected on *LRRK2* PD and non-*LRRK2* mutation, idiopathic PD (IPD) probands, and evaluated for suicide as cause of death among first-degree relatives. The odds of suicide among first-degree relatives was compared using a logistic generalised estimating equation, accounting for family membership, site and sex using Stata V.14 (StataCorp, 2015, Stata Statistical Software: Release 14. College Station, TX).

RESULTS

No *LRRK2* PD or IPD was known to commit suicide during the course of the study. (Study follow-up ranged from 0 to 5 years, and the mean duration among those with at least one follow-up visit was 3.4 years). *LRRK2* PD probands were more likely to report a death in a first-degree relative due to suicide compared with IPD (table 1) (8/142, 5.63% vs 3/388, 0.77%; p=0.002, Fisher's exact test). This association was maintained in the multivariate model accounting for family size and site: first-degree relatives of *LRRK2* PD 8/869 (0.92%) had greater odds of death by suicide compared with first-degree relatives of IPD 3/2336 (0.13%) (OR=7.19, 95% CI 1.91 to 27.07, p=0.004). While the main model included site of enrolment as a covariate, sensitivity analyses were performed post hoc to assess the contribution of death by suicide from each site. In univariate sensitivity analyses excluding each site, the increased odds of completed suicide in first-degree relatives of *LRRK2* PD was maintained when excluding the Columbia University Irving Medical Center site, but this result was no longer significant (OR=2.84, p=0.19).

Eight first-degree relatives of *LRRK2* PD who completed suicide comprised three parents, four siblings and one child; six were men, and all were from different families. Among the eight first-degree relatives of *LRRK2* PD that completed suicide, 5/8 completed suicide prior to their relative's PD onset, and 2/8 occurred after the onset of their relative's PD (age at death was not available for one first-degree relative of *LRRK2* PD). Mean±SD reported age at suicide in *LRRK2* PD first-degree relatives was 43.13±13.23 years (range: 17–59 years), and in IPD 43.00±14.80 years (range: 33–60 years). Although genotyping was not available for first-degree relatives of *LRRK2* PD, they had an a priori mutation risk of at least 50%.

DISCUSSION

Despite the small sample size and the limitations of the analysis, the excess of completed suicide in *LRRK2* first-degree relatives is provocative. Due to the short duration of follow-

up, it is not surprising that no suicides occurred in our *LRRK2* genotyped probands. However, death by suicide in an *LRRK2* patient has been reported in the setting of deep brain stimulation.[4] As all deaths occurred prior to study entry, we could not determine the genetic status of the first-degree relatives. The excess of suicides in *LRRK2* families may be an early non-motor manifestation of *LRRK2* PD, it may represent the interaction of additional genetic or environmental factors with *LRRK2*, or it may represent additional risk factors unrelated to *LRRK2*.

Of interest, most cases (7/8) were reported by probands recruited at the New York sites. The difference may be associated with cultural or medical factors affecting suicide completion or due to bias against reporting suicide as a cause of death. While the finding of cause of death was systematically queried, most other factors that may have contributed to the completed suicide were not. We, however, did explore the probands' reports of depression in their first-degree relatives with completed suicide. For those with available information (7/8 *LRRK2* first-degree relatives and 2/3 IPD first-degree relatives), 3/7 of the *LRRK2* first-degree relatives had a report of known depression compared with 2/2 of the IPD first-degree relatives, and this was not statistically significant (p=0.44). When history of depression was included in the main multivariate model comparing first-degree relatives of *LRRK2* PD and IPD, the odds of suicide remained higher in the *LRRK2* first-degree relatives (OR=9.36, p=0.005) suggesting that factors in addition to depression might be contributing to the discrepancy between groups. However, this analysis is limited by the small number of cases and proxy reporting of depression by the probands. Therefore, additional populations of *LRRK2* first-degree relatives should be studied to examine possible mediators, as well as the overall association between *LRRK2* mutations and completed suicide.

CONCLUSION

In sum, the results presented here, while provocative, must be considered with extreme caution. Our analysis was based on a family history of first-degree relatives given by probands. The analysis also did not account for a personal or familial history of behaviours that might place an individual at greater risk for completed suicide. As suicide is multifactorial, analysis of factors that may moderate this association, including impulsivity, affective disorders and substance abuse, should be interrogated in a subsequent study.[5] Replication and further study is therefore warranted, including robust instruments that assess potential risk factors and confounders for completed suicide.

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REFERENCES

1. Shanker V, Groves M, Heiman G, et al. Mood and cognition in leucine-rich repeat kinase 2 G2019S Parkinson's disease. Mov Disord 2011;26:1875–80. [PubMed: 21611978]

2. Saunders-Pullman R, Mirelman A, Alcalay RN, et al. Progression in the LRRK2-asssociated parkinson disease population. JAMA Neurol 2018;75:312–9. [PubMed: 29309488]
3. Alcalay RN, Mirelman A, Saunders-Pullman R. Parkinson disease phenotype in ashkenazi jews with and without LRRK2 G2019S mutations. movement disorders : official journal of the movement disorder society. Mov Disord 2013;28:1966–71. [PubMed: 24243757]
4. Puschmann A, Englund E, Ross OA, et al. First neuropathological description of a patient with Parkinson's disease and LrrK2 p.N1437H mutation. Parkinsonism Relat Disord 2012;18:332–8. [PubMed: 22154298]
5. Mann JJ, Arango VA, Avenevoli S, et al. Candidate endophenotypes for genetic studies of suicidal behavior. Biol Psychiatry 2009;65:556–63. [PubMed: 19201395]

Table 1

Summary of probands and first-degree relatives by site

Probands	***LRRK2* PD**	**IPD**	**Total**
Total (n)	142	388	530
Mount Sinai Beth Israel	40	96	136
Columbia University Irving Medical Center	37	95	132
Tel Aviv Medical Center	65	197	262
First-degree relatives	**FDRs of *LRRK2* PD**	**FDRs of IPD**	**Total**
Total (n)	869	2336	3205
Mount Sinai Beth Israel	209	593	802
Columbia University Irving Medical Center	215	540	755
Tel Aviv Medical Center	445	1203	1648
FDRs with suicide, n (% of FDRs)	8/869 (0.92)	3/2336 (0.13)	11/3205 (0.34)
Mount Sinai Beth Israel	2 (0.96)	2 (0.34)	4 (0.50)
Columbia University Irving Medical Center	5 (2.33)	0	5 (0.66)
Tel Aviv Medical Center	1 (0.22)	1 (0.08)	2 (0.12)

FDR, first-degree relative; IPD, idiopathic PD (no *LRRK2* mutation); *LRRK2*, leucine-rich repeat kinase 2 G2019S mutation; PD, Parkinson's disease.

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