Olfactory dysfunction in *LRRK2* G2019S mutation carriers

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ABSTRACT

Background: Olfactory dysfunction is an established nonmotor feature of idiopathic Parkinson disease (PD), which may precede disease onset. Olfaction is likely disturbed in patients with PD with leucine-rich repeat kinase (*LRRK2*) G2019S mutations, although the degree of impairment is debated. It is also unclear whether mutation carriers who have not yet manifested with PD have olfactory disturbances.

Methods: Thirty-one subjects with *LRRK2* G2019S mutation–related PD (PD-manifesting carriers [PD-MC]), 30 subjects with PD without mutations (PD noncarriers [PD-NC]), 28 mutation carrier family members (nonmanifesting carriers [NMC]), and 46 controls completed the University of Pennsylvania Smell Identification Test (UPSIT). Generalized estimating equations were applied to determine whether olfactory score was associated with PD and *LRRK2* mutation status.

Results: As expected, having PD was associated with impaired olfaction regardless of LRRK2 mutation status. More importantly, however, impaired olfaction was increased overall in LRRK2 carriers both with and without PD, though the impairment was only present in a subset of NMCs. Compared to controls, the mean score was lower among NMC (difference = −3.518, $p = 0.006$), MC (difference = −7.677, $p < 0.0001$), and idiopathic PD (PD-NC) (difference = −13.810, $p < 0.0001$). Olfaction was better among MC (PD-MC) than non-LRRK2 PD (PD-NC) (difference = 6.13, $p = 0.0012$). Group differences from the continuous analysis were maintained in dichotomous analysis stratifying at 15th percentile for age and gender.

Conclusion: Olfaction is impaired in *LRRK2* G2019S–mutation related PD, although less overall than other PD. Further, olfaction is impaired in a subset of *LRRK2* NMC, suggesting that olfaction may be a marker for development of PD in this group, and that longitudinal studies are warranted.

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GLOSSARY

CI = confidence interval; **EAS** = Einstein Aging Study; **MC** = manifesting carrier; **NC** = noncarriers; **NMC** = nonmanifesting carrier; **PD** = Parkinson disease; **UPDRS** = Unified Parkinson's Disease Rating Scale; **UPSIT** = University of Pennsylvania Smell Identification Test.

Parkinson disease (PD) due to mutations in the *LRRK2* gene appears to more closely mimic idiopathic PD than any other genetic etiology.[1] Yet there are still gaps and uncertainty in our knowledge of *LRRK2* clinical expression. For example, there is controversy regarding the clinical course of *LRRK2* PD and whether progression is similar or less rapid compared with idiopathic PD.[2–4] The range and severity of nonmotor features associated with *LRRK2* mutations is also not well-defined. Several studies suggest that olfactory disturbance is a feature of *LRRK2* PD[3,5–8] but the degree of the impairment is debated. Finally, it is uncertain whether carriers who have not yet developed PD have abnormal olfaction,[6,7] and whether this may be an endophenotype or trait of carrying the mutated *LRRK2* gene.

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Hyposmia is a common nonmotor feature of PD, present in 70%–100% of subjects with PD[9,10] and may discriminate PD from atypical forms such as vascular parkinsonism and corticobasal degeneration.[11–13] Loss of neurons and Lewy body deposition are also noted in the anterior olfactory bulb in PD.[14] Olfaction has been reported as normal in some genetic etiologies of parkinsonism, such as that due to *parkin* mutations,[15] but is abnormal in *PINK1* and glucocerebrosidase-related PD.[16–18] However, the association with olfaction in *LRRK2* PD is less clear: olfaction has been reported as normal,[19] not as significantly affected, or as consistently impaired as in idiopathic PD.[3,5–8] Olfactory loss may precede clinical PD by at least 4 years,[20] and thus may be a marker of developing PD. Reports of olfaction in *LRRK2* mutation carriers without PD, a group that is at increased risk of developing PD, are both limited and conflicting.[6,7] In order to systematically examine whether olfaction is affected in *LRRK2* PD compared with idiopathic PD, and determine whether olfaction is impaired in mutation carriers who have not yet manifested PD, we studied *LRRK2* G2019S mutation carriers with PD-MC (manifesting carriers [MC]), unaffected family members with *LRRK2* mutations (nonmanifesting carriers [NMC]), subjects with PD without *LRRK2* mutations (PD noncarriers, PD-NC), and healthy controls without a family history of PD (controls).

METHODS Sixty-one subjects with PD (31 with *LRRK2* G2019S mutations [PD-MC] and 30 without [PD-NC]), 28 mutation carrier family members (NMC), and 46 controls were recruited from parent studies of Genetics and PD at Beth Israel Medical Center and the Einstein Aging Study (EAS) at Albert Einstein College of Medicine. At Beth Israel, all study subjects were systematically examined by movement disorders specialists. A diagnostic checklist was completed, and only those subjects rated as having met stringent diagnostic criteria for PD[21] were included. One family member who was determined to have PD was not diagnosed prior to the examination, and is included in the PD-MC group. Family members with G2019S mutations as well as spouse and laboratory controls without a family history of PD were included. At the EAS, formal neurologic evaluation including completion of the Unified Parkinson's Disease Rating Scale (UPDRS)[22] was performed by a physician; for this study, a subset of elderly controls without parkinsonian features and with a Clinical Dementia Rating Scale score of less than 1 were included. Any potential subject who had a known respiratory tract infection or active allergies was also excluded from the study.

The encapsulated odor University of Pennsylvania Smell Identification Test (UPSIT) was self-administered by using standard 40-odor identification[23] either at the time of the visit or at the subject's home, and returned by mail. Subjects were instructed to choose a response from the 4 choices listed. Tests which included incomplete responses were excluded from the analysis.

DNA was available from blood or buccal swab drawn at the parent study. *LRRK2* genotyping was performed as previously described.[24] All subjects were blinded to their mutation status except for 2 mutation carriers with PD and one nonmanifesting mutation carrier who had undergone clinical genetic testing.

Demographic characteristics and clinical scores among groups were summarized with descriptive statistics. Raw UPSIT scores were calculated as the number of correct identifications, ranging from 0 to 40, with 40 representing perfect olfaction. Analysis was performed first on the raw UPSIT scores as the primary outcome. Scores were also categorized using normative data for age and gender as previously reported by Doty,[25] with a dichotomous cut at the 15th percentile.[26] Generalized estimating equations (GEE) were applied to account for the correlations among measurements of subjects from the same family and to compare continuous UPSIT scores among the different groups, adjusting for age and gender, with a logistic link for the dichotomized UPSIT score. Analyses were performed using SAS 9.1 (SAS Institute Inc., Cary, NC).

Standard protocol approvals, registrations, and patient consents. The study procedures were approved by the respective internal review boards at Beth Israel Medical Center and Albert Einstein College of Medicine, and all subjects gave informed consent.

RESULTS Demographic and clinical features are shown in the table. The non-*LRRK2* PD (PD-NC) and MC (PD-MC) groups did not differ by age, duration of disease, UPDRS score at time of visit, or current or prior smoking. The NMC did not differ compared with controls in regards to age, gender, or current and prior smoking. However, compared with the controls, those with PD were older ($p = 0.024$). The MC and the NMC were not different in age, gender, or smoking status.

Analysis of continuous UPSIT scores is shown in the table and in the figure. As anticipated, older age was associated with lower UPSIT scores (worse olfaction, $p < 0.0001$). Prior smoking and gender were not associated with worse olfaction. In the GEE model adjusting for age, gender, and taking family relationship into account, both PD and *LRRK2* PD as well as carrying the *LRRK2* mutation without manifesting symptoms were associated with worse olfaction: compared to controls, the mean score was lower among NMC (mean estimate of difference = −3.518, 95% confidence interval [CI] −6.004, −1.03, $p = 0.006$), PD-MC (difference = −7.677, 95% CI −10.507, −4.846, $p < 0.0001$) and PD-NC (difference = −13.810, 95% CI −16.824, −10.795, $p < 0.0001$) as well as all PD (PD-NC

Table Clinical features and UPSIT scores

	PD-NC (mutation negative) (n = 30)	PD-MC (mutation positive) (n = 31)	*LRRK2*+ NMC (n = 28)	Controls (n = 46)
Age at examination, y, mean ± SD (range)	63.4 ± 7.8 (48-77)	64.7 ± 9.8 (33-81)	58.0 ± 22.4 (18-84)	57.9 ± 16.7 (25-99)
Gender, % (n) men	56.7 (17/30)	48.4 (15/31)	46.4 (13/28)	48.8 (22/46)
Current smoker, % (n)	3.45 (1/30)	3.23 (1/31)	3.85 (1/28)	0
Past smoker, % (n)	37.9 (11/29)	35.5 (11/31)	30.8 (8/28)	30.4 (14/46)
PD duration, y, mean ± SD (range)	9.3 ± 5.5 (2-21)	9.9 ± 6.7 (0-29)	—	—
Motor UPDRS, mean ± SD (range)	13.1 ± 9.4 (3-48)	12.3 ± 10.9 (0-45)	—	—
Continuous UPSIT scores, mean ± SD (range)	18.8 ± 8.05 (5-36)	24.8 ± 7.08 (9-38)	30.1 ± 7.55 (10-39)	33.6 ± 3.82 (18-39)
Proportion hyposmic (<15th %ile), % (n)	83.3 (25/30)	58.1 (18/31)	35.7 (10/28)	6.5 (3/46)

Abbreviations: PD-MC = PD subject manifesting carrier of *LRRK2* G2019S mutation; NMC = nonmanifesting carrier; PD-NC = Parkinson disease, not G2019S carrier; UPDRS = Unified Parkinson's Disease Rating Scale; UPSIT = University of Pennsylvania Smell Identification Test.

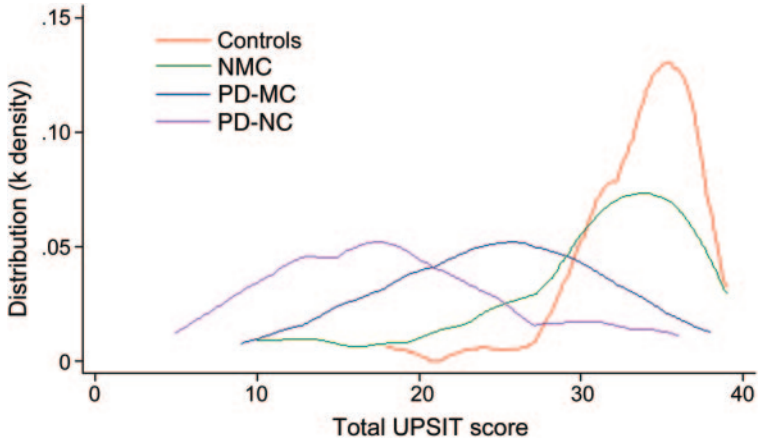
and PD-MC combined) (difference = −8.984, 95% CI −11.512, −6.457, $p < 0.0001$).

Olfaction was better among PD-MC than non-*LRRK2* PD (PD-NC) (difference = 6.13, 95% CI 2.422, 9.845, $p = 0.0012$).

While harboring the G2019S mutation was associated with lower scores among both NMC and PD-MC, the PD-MC group had a worse mean score than NMC (difference = −4.159, 95% CI −7.943, −0.376, $p = 0.0312$). The expected interaction between harboring the *LRRK2* mutation and having PD ($p < 0.0001$) was observed.

In the analysis of categorical UPSIT scores (based on age and gender normative data at the 15th percentile; table), group differences which were noted for the raw UPSIT score were maintained in the dichotomous analysis: *LRRK2* PD subjects (PD-MC) were more likely to be hyposmic than both NMC (OR = 3.05, $p = 0.032$) and controls (OR = 25.69, $p < 0.0001$), but less likely than non-*LRRK2* PD subjects (PD-NC) (OR = 0.27, $p = 0.034$); *LRRK2* NMC were more likely to be hyposmic than controls (OR = 8.44, $p = 0.004$).

Figure Kernel density plot demonstrating distribution of University of Pennsylvania Smell Identification Test (UPSIT) scores in manifesting carriers, Parkinson disease (PD), nonmanifesting carriers, and controls



DISCUSSION Olfactory dysfunction is established as a common nonmotor feature of PD[9,27,28] and there is a correlation between olfactory dysfunction and [99mTc] TRODAT-1 SPECT dopamine transporter density.[29] Screening of first-degree relatives who have not developed motor features of PD, but have abnormal dopamine metabolism on PET, suggests that impairment in olfaction precedes clinical PD and is associated with dopaminergic cell loss.[30–32] In this, the largest series of olfaction in *LRRK2*-related PD studied to date, our data support that olfactory disturbances, while less severe than idiopathic PD, are also a prominent feature of *LRRK2* G2019S–related PD.[33] Further, our data suggest that olfactory dysfunction is a feature of carrying the *LRRK2* G2019S mutation that may occur without manifesting motor features. Because olfactory disturbances are not as severe in NMC overall compared to MC, and because this was a cross-sectional study, it is unclear whether all NMC with olfactory disturbances will evolve to develop PD or whether they represent an intermediate endophenotype that is not an immediate precursor to development of PD.

The pathophysiologic basis of *LRRK2* PD is still not well understood: most autopsy reports demonstrate α-synuclein deposition with Lewy bodies as well as nigral degeneration.[6,34] However, a range of pathology is noted, with few cases demonstrating ni-

gral degeneration in isolation[35] and others showing tau inclusions.[36] In idiopathic PD, Lewy bodies and Lewy neurites are noted in the olfactory bulb; further, olfactory pathology is thought to occur as an early or initial event according to the staging schema for PD progression proposed by Braak et al.[37] In the limited *LRRK2* cases reported, α-synuclein accumulation in the rhinencephalon was shown in 4 cases of G2019S mutation PD[6] and Lewy body deposition in the olfactory bulb was demonstrated in one *LRRK2* Y1699C mutation case.[19] These findings suggest that the effects of mutant *LRRK2* include olfactory pathology, at least in a subset of carriers. Hence abnormal olfaction noted in our unaffected mutation carriers could represent the first stage in progression to PD. However, the temporal characteristics of *LRRK2*-related pathology are not established and may not follow Braak's staging schema. Evaluation of other nonmotor features, including transcranial sonography, and functional imaging and longitudinal follow-up will help determine whether olfactory involvement is necessarily part of inexorable progression of PD pathology or may represent a more restricted gene effect.

Similar to *PINK1*[17] and glucocerebrosidase-associated PD,[16,18] but unlike PD due to *parkin* mutations,[15] most[8] but not all[19] *LRRK2* mutation studies support the idea that olfaction is impaired in this genetic form.[8] While the degree of olfactory pathology has not been formally quantified in PD and *LRRK2* PD, our clinical data support the notion that *LRRK2* pathology may not be as extensive. A meta-analysis of *LRRK2* mutation subjects with olfactory testing demonstrated that only 51% of *LRRK2* G2019S mutation patients had significant olfactory loss.[3] By virtue of the study design, however, *LRRK2* cases could not be readily compared with controls or other PD cases. Whereas this suggests better olfaction than in idiopathic PD, it also highlights the methodologic concerns about how to rate olfactory abnormalities, and whether these should be considered relative to population norms, or whether each research group reporting olfactory scores needs to develop a large control sample.

Several reports have analyzed G2019S family members, with heterogenous results.[6–8] Studies to compare olfaction between NMCs and family members who are noncarriers are currently underway and should help determine whether olfactory disturbance segregates with *LRRK2* or whether it represents an intrafamilial abnormality, suggesting other possibly modifying PD genes.

A potential limitation of our study is that while we have sampled one of the largest groups of NMCs, including elderly NMCs, we did not have a large control sample for every decade and gender. Hence, we chose to report both continuous data compared with our laboratory controls as well as categorical normative data obtained through studies of 3,928 (1,819 men and 2,109 women) US controls.[25]

By demonstrating a difference between nonmanifesting carriers and controls, we suggest that in a subset of *LRRK2* mutation carriers, UPSIT may identify nonmotor features of preclinical PD. However, we did not have enough NMCs to define subgroups; only 35% of NMCs fell below the 15th percentile for age and gender and thus some carriers may not have olfactory disturbances or may have only minimal olfactory changes. Longitudinal studies are necessary to determine the temporal relationship between olfaction and the development of motor signs.[28,32] It is hoped that better understanding of motor and nonmotor features of *LRRK2* PD will shed light on the pathophysiology of this genetic PD subtype.

AUTHOR CONTRIBUTIONS

Dr. Saunders-Pullman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, obtaining funding. K. Stanley: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. Dr. Wang: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. San Luciano: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Shanker: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Hunt: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. Severt: drafting/revising the manuscript, acquisition of data. D. Raymond: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Ozelius: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Lipton: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis, study supervision, obtaining funding. Dr. Bressman: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding.

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DISCLOSURE

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rospasm Research Foundation, and the National Spasmodic Dysphonia Association; is listed as an author on patents re: Torsin, Torsin genes and methods of use, and Nucleic acids, methods and kits for the diagnosis of DYT6 primary torsion dystonia; receives research support from the NIH, the Dystonia Medical Research Foundation, and the Bachmann Strauss Dystonia Parkinson Foundation; and receives royalties from Athena Diagnostics, Inc. for a patent re: Torsin, Torsin genes and methods of use. Dr. Lipton serves on scientific advisory boards for Allergan, Inc., Merck Serono,, Neuralieve, Inc., and Pfizer Inc.; has received funding for travel from the American Headache Society, Cognimed, Diamond Headache Clinic Research, Market Force Communications, Merck Serono, Migraine Research Foundation, Scienta, and Talley Management; serves as Associate Editor of *Cephalalgia* and on the editorial boards of *Neurology*® and *Headache*; receives royalties from publishing *Headache in Clinical Practice* (Isis Medical Media, 2002), *Headache in Primary Care* (Isis Medical Media, 1999), *Wolff's Headache* (Oxford University Press, 2001, 2008), *Managing Migraine: A Physician's Guide* (BC Decker, 2008), and *Managing Migraine: A Patient's Guide* (BC Decker, 2008); has received speaker honoraria from the National Headache Foundation, the University of Oklahoma, the American Academy of Neurology, the Annenberg Foundation, Merck Serono, GlaxoSmithKline, and Coherex Medical; serves as a consultant for Allergan, Inc., Autonomic Technologies, MAP Pharmaceuticals, Inc., Neuralieve, Inc., and Novartis; receives/has received research support from AstraZeneca, Ortho McNeil, GlaxoSmithKline, Merck Serono, ProEthic Pharmaceutical, Inc., Advanced Bionics, the NIH/NIA, St. Jude Medical, the Migraine Research Foundation, and the National Headache Foundation; and holds stock options in Minster Pharmaceuticals plc. Dr. Bressman serves on scientific advisory boards for the Bachmann Strauss Dystonia and Parkinson's Foundation, the Michael J Fox Foundation for Parkinson's Research, and the Dystonia Medical Research Foundation; holds a patent re: THAP1 gene testing; and receives research support from the NIH and the Michael J Fox Foundation for Parkinson's Research.

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