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Self-report of cognitive impairment and Mini-Mental State Exam performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease

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Abstract

While little is known about risk factors for cognitive impairment in early onset Parkinson disease (EOPD), postmortem studies have shown an association between dementia with Lewy bodies (DLB) and glucocerebrosidase (*GBA*) mutation. We compared Mini-Mental State Examination (MMSE) performance and self-reported cognitive impairment in 699 EOPD participants genotyped for mutations in parkin (*PRKN*), leucine-rich repeat kinase-2 (*LRRK2*), and *GBA*. Logistic regression was used to assess the association between reported cognitive impairment and MMSE score, as well as between *GBA* group membership and self-reported impairment and MMSE. *GBA* carriers reported more impairment, but MMSE performance did not differ among genetic groups. Detailed neuropsychological testing is required to explore the association between cognitive impairment and *GBA* mutations.

Keywords

Parkin; Leucine-rich repeat kinase-2; Glucocerebrosidase; Parkinson; Cognition; Mini-Mental State Examination; Genetics

INTRODUCTION

Early onset Parkinson disease (EOPD) is defined as disease onset before age 40 or 50 years (Butterfield, Valanis, Spencer, Lindeman, & Nutt, 1993; Kostic et al., 1994; Schrag & Schott, 2006). It has been estimated that up to 10% of PD patients have an age at onset (AAO) of ≤40 years (Schrag, Ben-Shlomo, Brown, Marsden, & Quinn, 1998). EOPD is

probably a multifactorial disease caused by an interaction of environmental and genetic factors. Overall, the vast majority of EOPD patients do not carry a known genetic risk factor associated with PD (Macedo et al., 2009), but specific genetic mutations have been identified in a subset of patients. While in rare familial cases mutations in alpha synuclein (*SNCA*), *DJ-1*, and *PINK-1* may be found, mutations in parkin (*PRKN*), leucine-rich repeat kinase-2 (*LRRK2*), and glucocerebrosidase (*GBA*) are more common, especially in selected populations—for example, *LRRK2* and *GBA* mutations in Ashkenazi Jews. Mutations in the *PRKN* gene are found in approximately 10% of EOPD patients and are inversely associated with AAO (Clark et al., 2007a). Mutations have been described in the homozygous, compound heterozygous, and heterozygous states, but the role of heterozygous mutations remains controversial.

Although previous studies have shown that dementia is uncommon in EOPD with AAO ≤50 (Kostic et al., 1994) the pattern and extent of cognitive changes in EOPD and associated risk factors have not been described. While mutations in *SNCA* are associated with dementia (Schrag & Schott, 2006) it is unknown whether mutations more commonly seen in EOPD, in *PRKN*, *LRRK2*, or *GBA*, convey a risk for cognitive impairment as well.

A family-based study comparing *PRKN* carriers (n = 21) to EOPD patients without mutations did not find differences in neuropsychological performance (Lohmann et al., 2009). To our knowledge, the cognitive performance of EOPD with *LRRK2* or *GBA* mutations has not been reported in large studies; however, we and others have reported that *GBA* mutations are associated with dementia with Lewy bodies (DLB) at autopsy (Clark et al., 2009; Neumann et al., 2009) and therefore may represent a risk for cognitive impairment.

The current study assessed in the largest sample of nondemented EOPD cases reported to date whether mutations in the *PRKN*, *LRRK2*, and *GBA* genes are associated with self-reported cognitive impairment. We further compared performance across the mutation groups on the Mini-Mental State Exam (MMSE), a commonly used cognitive screening test in PD centers (Dubois et al., 2007).

METHOD

Participants

Cases with AAO ≤50 (n = 699) participating in the Consortium On Risk for Early-Onset Parkinson Disease (CORE-PD) study were recruited from 13 sites (Clark et al., 2007b). Institutional review boards at all participating sites approved the protocols and consent procedures. PD cases were required to have an MMSE score >23 so that they could accurately provide their own medical history and family history of PD in their relatives. Data collected on each case included demographic information, AAO, the Unified Parkinson's Disease Rating Scale (UPDRS) completed by a movement disorders specialist (Fahn, Elton, & Committee, 1987), MMSE (Folstein, Folstein, & McHugh, 1975), family history of PD using a previously validated interview, and a blood sample from which DNA was isolated and examined for mutations in *PRKN*, *LRRK2*, and *GBA*. Examiners were trained by a certified neuropsychologist (E.C.) in administrating the MMSE and were unaware of cases' genetic status. Cases were subsequently divided into five groups based on mutation status: (a) noncarriers of mutations of any of the three genes, (b) *PRKN* heterozygotes, (c) *PRKN* homozygotes and compound heterozygotes combined, (d) *LRRK2* mutation carriers, and (e) *GBA* mutation carriers.

Molecular genetic analysis

Parkin—Cases were screened for *PRKN* mutations by denaturing high-performance liquid chromatography (DHPLC; WAVE Transgenomic), as previously described (Pigullo et al., 2004). Amplicons were either directly sequenced (n = 126) or analyzed (n = 573) using a *PRKN* genotyping array (Clark et al., 2007a) in DNA samples with abnormal DHPLC elution profiles. Cycle sequencing was performed on the purified PCR product as per the manufacturer's instructions (BigDye, Applied Biosystems). Products were processed on an ABI3700 genetic analyzer. Chromatograms were viewed using Sequencher (Genecodes), and sequence variants were determined. To identify genomic deletions and exon rearrangements in *PRKN*, semiquantitative multiplex polymerase chain reaction (PCR) was performed as previously described (Clark et al., 2006a).

LRRK2 and GBA—DNA samples from the majority of the cases (n = 506) were analyzed using a previously described genotyping chip (Clark et al., 2007a; Asper Biotech, Tartu, Estonia). For the remaining 193 cases, *LRRK2* genotyping was performed using matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry (Sequenom) as previously described (Clark et al., 2006b). All samples analyzed by either the MALDI-TOF or the genotyping chip were examined for the *LRRK2* mutations G2019S, R1441C, I2020T, and Y1699C. The rest of the *GBA* samples were genotyped by direct sequencing. All samples were tested for the N370S and L444P *GBA* mutations.

Statistical analyses

Self-report of cognitive impairment, MMSE performance, and demographic and disease characteristics of the five mutation status groups were compared using analysis of variance (ANOVA), Kruskal–Wallis, and chi square tests as appropriate. The effect size of MMSE performance was calculated using the probabilistic index comparing noncarriers to each mutation group separately. A value of .5 indicates a 50% chance of a score coming from a mutation carrier group to be higher than a score from the noncarrier group (i.e., no difference between the groups). Values closer to 0 indicate greater likelihood that noncarriers scored better than mutation carriers (Acion, Peterson, Temple, & Arndt, 2006).

The association between cases' report of cognitive impairment, defined as a response of two ("moderate memory loss with disorientation and moderate difficulty handling complex problems") or greater on Item I of the UPDRS Part I and MMSE performance, was tested using a logistic regression model where report of cognitive impairment was the dependent variable and MMSE performance the independent covariate.

Finally, we used a logistic regression model to test the association between *GBA* mutation status (dependent) and self-report of cognitive impairment adjusting for Jewish descent (defined as all four grandparents reporting Jewish ancestry), MMSE score, and self-reported depression, defined as a response of two ("sustained depression for >1 week") or more on Item III on the UPDRS Part I (Levy et al., 2002). Self-reported depression was added to the model given that depression may affect one's awareness or insight into their cognitive performance,

RESULTS

A total of 103 cases carried a genetic mutation: A total of 23 were *PRKN* heterozygotes, 20 were *PRKN* homozygotes/compound heterozygotes, 20 were G2019S *LRRK2* carriers (19 heterozygotes, one homozygote; no other pathogenic *LRRK2* mutations were found), and 37 were *GBA* carriers (12 L444P heterozygotes, 24 N370S heterozygotes, and 1 N370S homozygote). A total of 3 cases carried mutations in more than one gene (one *PRKN*

heterozygote-*LRRK2* carrier, one *PRKN* heterozygote *GBA* carrier, and one *LRRK2-GBA* carrier) and were excluded from the analyses. A total of 7 cases were administered the MMSE in Spanish. The median MMSE scores, the effect size of MMSE performance (in each mutation group compared to noncarriers), and disease characteristics of the genetic groups are presented in Table 1.

The UPDRS Part I was available for 617 cases. A larger proportion of *GBA* carriers reported cognitive impairment (score of 2 or more) than all other genetic groups (21.9%, 7/32, $p < .001$). Subjective cognitive impairment on the UPDRS Item I, which was reported by 5% of cases ($n = 31$) was associated with a lower score on the MMSE. For each 1-point decline on the MMSE the odds of reporting cognitive impairment increased by 38% (odds ratio, OR = 0.62; 95% confidence interval, CI: 0.51–0.76, $p < .001$, logistic regression).

A total of 57% (396/699) of participants obtained a score of 30 on the MMSE. The mean score was 29.2, the median 30. Mistakes were most often made on the long-term memory items (19.1% of all cases made at least one error in recall), working memory (10.3% of all cases made at least one error), naming the county (8.9%), and visuospatial orientation (8.6% made an error copying intersecting pentagons). There were no significant differences among the genetic groups in overall MMSE performance (Table 1) or on individual item performance.

In a logistic regression model (Table 2) including *GBA* carriers and noncarriers, report of cognitive impairment on the UPDRS-I and Jewish ancestry predicted *GBA* mutation group membership after adjusting for reported depression, but MMSE performance did not.

DISCUSSION

This is the largest study reported to date assessing self-reported cognitive impairment and MMSE performance in EOPD. Individuals with EOPD are usually highly functional—for example, working and driving; consequently the identification of risk factors for cognitive impairment in this group is vital (Schrag et al., 1998). Here, we did not find an association between MMSE performance and the most frequent genetic mutations found in EOPD; however, *GBA* carriers' self-report of more cognitive complaints than any other mutation carrier group or noncarriers may be viewed, in the context of postmortem studies suggesting an association between *GBA* mutations and DLB (Clark et al., 2009; Neumann et al., 2009), as a possible early marker for cognitive decline.

The strengths of our study lie in its large size, which is important given that most EOPD individuals are not mutation carriers. Limitations include the tools used to assess cognitive dysfunction and self-report cognitive impairment. While the MMSE is perhaps the most commonly used screen for cognitive decline, its lack of sensitivity is well documented. Our novel use of Item I of the UPDRS questionnaire as a measure of subjective cognitive changes may also represent a weakness in the study; however, subjective memory complaint assessed via a single question ("Do you have complaints about your memory?") has been found to be predictive of incident Alzheimer's disease with an average follow-up of 3.2 years in healthy elders in whom no cognitive impairment was identified (Geerlings, Jonker, Bouter, Ader, & Schmand, 1999). Furthermore, self-report of cognitive impairment was associated with lower performance on the MMSE, demonstrating the validity of the UPDRS questionnaire. Finally, the participants included likely represent a restricted sample in that participants scoring < 24 on the MMSE were excluded.

We have shown that self-reported cognitive impairment is associated with *GBA* mutations and with lower performance on the MMSE. MMSE performance was not significantly different among mutation groups, either because there are no cognitive differences among

the mutation groups, or because the MMSE was not sensitive enough to detect the *GBA* carriers' cognitive impairment. Future studies utilizing comprehensive neuropsychological assessment measures would more fully characterize the nature of these cognitive complaints.

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Table 1

MMSE performance and disease characteristics of 696 probands stratified by genetic group[1]

	Non-carriers (n=596)	***Parkin* heterozygotes (n=23)**	**Carriers of 2 *parkin* mutations (n=20)**	***LRRK2* carriers (n=20)**	***GBA* carriers (n=37)**	**Sig.[2]**
Self report of cognitive impairment	4.2% (22)[a]	10.0% (2)[a]	0[a]	0[a]	21.9% (7)[b]	<0.001
Median MMSE score	30	29	29	30	30	NS
MMSE performance effect size[3]		0.40	0.40	0.42	0.50	
Age (years)	52.0 (8.6)[a]	48.8 (8.0)[a,b]	46.1 (13.4)[b]	54.9 (7.9)[a]	54.4 (4.9)[a]	<0.001
AAO (years)	41.9 (6.3)[a]	38.9 (9.2)[a]	28.7 (9.3)[b]	43.6 (4.8)[a]	42.3 (6.8)[a]	<0.001
Disease duration	10.2 (7.3)[a]	9.9 (9.4)[a]	17.7 (13.0)[b]	11.3 (7.6)[a]	12.1 (7.3)[a]	<0.001
UPDRS-III	19.9 (11.4)	21.6 (12.9)	22.6 (13.0)	19.8 (14.7)	23.8 (11.3)	NS
Jewish ancestry	7.4% (44)	0	0	65.0% (13)	35.1% (13)	<0.001
Levodopa daily dose (mg)	469 (470)	276 (334)	667 (911)	420 (407)	559 (347)	NS
Education (years)	15.6 (2.8)	14.8 (3.5)	13.9 (2.8)	16.0 (3.2)	15.7(3.0)	NS

Values are means and standard deviations (in parentheses), except for MMSE (median) and Jewish ancestry where values are in percent and numbers (in parentheses). Values with different superscript letters differ significantly on *post-hoc* testing

[1] Excluding 3 probands with more than one genetic mutation

[2] Statistical significance was calculated using ANOVA, except for MMSE performance (Kruskal Wallis), and Jewish ancestry (chi square).

[3] Effect size represents the likelihood of members of the genetic group to obtain a higher MMSE score than the non-carrier group

Table 2

Logistic regression model predicting *GBA* mutation group membership versus non-carriers including 560 cases

Variable	OR	95% confidence interval	p value
Self reported cognitive impairment	5.9	2.0–17.8	0.001
MMSE performance	1.05	0.77–1.42	0.78
Self reported depression	0.46	0.1–2.2	0.33
Jewish Ancestry	7.9	3.4–18.2	<0.001