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Original Investigation

Cognitive and Motor Function in Long-Duration *PARKIN*-Associated Parkinson Disease

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IMPORTANCE Data on the long-term cognitive outcomes of patients with *PARKIN*-associated Parkinson disease (PD) are unknown but may be useful when counseling these patients.

OBJECTIVE Among patients with early-onset PD of long duration, we assessed cognitive and motor performances, comparing homozygotes and compound heterozygotes who carry 2 *PARKIN* mutations with noncarriers.

DESIGN, SETTING, AND PARTICIPANTS Cross-sectional study of 44 participants at 17 different movement disorder centers who were in the Consortium on Risk for Early-Onset PD study with a duration of PD greater than the median duration (>14 years): 4 homozygotes and 17 compound heterozygotes (hereafter referred to as carriers) and 23 noncarriers.

MAIN OUTCOMES AND MEASURES Unified Parkinson Disease Rating Scale Part III (UPDRS-III) and Clinical Dementia Rating scores and neuropsychological performance. Linear regression models were applied to assess the association between *PARKIN* mutation status and cognitive domain scores and UPDRS-III scores. Models were adjusted for age, education, disease duration, language, and levodopa equivalent daily dose.

RESULTS Carriers had an earlier age at onset of PD ($P < .001$) and were younger ($P = .004$) at time of examination than noncarriers. They performed better than noncarriers on the Mini-Mental State Examination ($P = .010$) and were more likely to receive lower scores on the Clinical Dementia Rating ($P = .003$). In multivariate analyses, carriers performed better than noncarriers on the UPDRS-III ($P = .02$) and on tests of attention ($P = .03$), memory ($P = .03$), and visuospatial ($P = .02$) cognitive domains.

CONCLUSIONS AND RELEVANCE In cross-sectional analyses, carriers demonstrated better cognitive and motor performance than did noncarriers with long disease duration, suggesting slower disease progression. A longitudinal follow-up study is required to confirm these findings.

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PARKIN mutations are the most common genetic mutations associated with early-onset Parkinson disease (EOPD), defined by an age at onset of 50 years or younger.[1] Two cross-sectional studies[2,3] that examined the cognitive performance of patients with EOPD found similar neuropsychological results between homozygous and compound heterozygous (H/CH) carriers and noncarriers of *PARKIN* mutations. However, it has been hypothesized that H/CH carriers are less likely than noncarriers to develop dementia and that longer follow-up is required to differentiate between the cognitive performances of H/CH carriers and those of noncarriers.[4] To explore this hypothesis, we repeated our analyses of the Consortium on Risk for Early-Onset PD (CORE-PD) study after recruiting additional participants and restricting the analyses to those with a higher than median (>14 years) disease duration. Using cross-sectional data, we approximated long-term follow-up by examining the cognitive profiles of individuals with PD of long duration, using a larger sample of patients with EOPD than we previously reported.[2]

Methods

Participants

Participants with EOPD defined by an age at onset of 50 years or younger were recruited from 13 movement disorder centers participating in the CORE-PD study as previously described.[5,6] Four sites (in San Juan, Puerto Rico; Albany, New York; Atlanta, Georgia; and Portland, Oregon) were later added to increase the number of H/CH carriers and noncarriers with EOPD. The institutional review boards at all the participating sites approved the protocols and consent procedures. We performed detailed examinations, including a neuropsychological battery on 178 probands with EOPD who had mutations in *PARKIN* and glucocerebrosidase (*GBA*), and on a subset of participants without known mutations.[6] To approximate long-term follow-up, we examined the distribution of PD duration and selected individuals with a disease duration greater than the median duration (ie, 14 years). We excluded carriers of *GBA* and *LRRK2* mutations. Because of the controversial role of heterozygous *PARKIN* mutations,[6-8] heterozygous carriers were also excluded. The analyses were performed on 4 homozygotes and 17 compound heterozygotes who carry 2 mutations in *PARKIN* (ie, 21 carriers) and 23 noncarriers of mutations in *PARKIN*, *PINK-1*, *DJ-1*, *LRRK2*, or *GBA*.[5] Of the 44 participants included in the final analysis, 38 were previously reported.[2] Of the 6 new participants, 2 were carriers, and 4 were noncarriers.

Molecular Genetic Analyses

Participants were genotyped for *PARKIN*, *GBA*, *LRRK2*, *PINK-1*, and *DJ-1* as previously described.[5,9,10] Beginning in 2010, we used multiplex ligation-dependent probe amplification (MLPA)[7] for newly recruited probands and for all probands recruited prior to 2010 with point mutations or dosage changes. All deletions and duplications identified via MLPA were verified using real-time polymerase chain reaction. All probands with *PARKIN* mutations detected via the resequencing chip or with dosage detected via MLPA have had full sequencing of *PARKIN* exons and MLPA if not previously performed.

Clinical and Neuropsychological Evaluation

The clinical evaluation of CORE-PD participants has been previously described.[6,11] In brief, it included the Unified Parkinson Disease Rating Scale (UPDRS),[12] which was performed in the "on" state, the Mini-Mental State Examination, the Clinical Dementia Rating,[13] and a neuropsychological battery. The neuropsychological battery used in our study was composed of measures corresponding to 5 cognitive domains: psychomotor speed, attention, memory, visuospatial function, and executive function (eTable 1 in Supplement).[2,11,14,15] The battery included measures that could be administered in English or Spanish. Each participant was assigned a clinical consensus diagnosis based on medical history, neurological examination, neuropsychological performance, and functional impairment, without knowledge of genetic status.[11] Participants were rated as being cognitively normal, as having mild cognitive impairment,[16] or as being demented.[11]

Statistical Analysis

Individual neuropsychological test scores were transformed to create *z* scores using means and standard deviations of the entire sample of PD cases. Composite scores for each domain were computed by averaging the mean *z* scores from the individual tests comprising each domain.[11] Demographic data, disease characteristics, Mini-Mental State Examination scores, Clinical Dementia Rating scores, and neuropsychological test performances were compared between carriers and noncarriers using the Fisher exact test, the χ^2 test, and the *t* test as appropriate. Linear regression models were constructed to test the association between genetic status (predictor) and UPDRS Part III (UPDRS-III) and cognitive domain scores (outcomes), adjusting for age, duration of PD, education (truncated at 20 years), levodopa equivalent daily dose, and the language that the tests were administered in (ie, Spanish or English).

Results

The demographic and clinical characteristics of the participants stratified by *PARKIN* genetic status are shown in **Table 1**. The H/CH carriers had an earlier age at onset of PD and were younger at time of the examination than the noncarriers. They performed better on the Mini-Mental State Examination and were more likely to receive lower Clinical Dementia Rating scores (indicating better functional status) than noncarriers. Mean raw scores on individual neuropsychological tests are reported in eTable 2 in Supplement.

In models adjusted for age, sex, disease duration, education, levodopa equivalent daily dose, and language (**Table 2**), the *PARKIN* mutation status of H/CH carriers was associated with better performance on the UPDRS-III ($P = .02$) and on tests of attention ($P = .03$), memory ($P = .03$), and visuospatial ($P = .02$) cognitive domains compared with noncarriers. Better cognitive performance in each of the cognitive domains was

Table 1. Clinical and Demographic Characteristics of Noncarriers and Carriers of 2 *PARKIN* Mutations

Characteristic	Noncarriers[a] (n = 23)	Carriers[b] (n = 21)	*P* Value
Age, mean (SD), y	61.5 (6.4)	53.1 (11.5)	.004
Age at onset, mean (SD), y	40.2 (4.0)	26.6 (10.0)	<.001
Disease duration, mean (SD), y	21.3 (4.2)	26.5 (9.7)	.02
Education, mean (SD), y	15.7 (4.2)	13.5 (2.8)	.05
Neuropsychological testing in Spanish, No. (%) of participants	3 (13.0)	5 (23.8)	.45
UPDRS-III score, mean (SD)	27.8 (10.1)	21.0 (7.0)	.02
Levodopa equivalent daily dose, mean (SD), mg	811 (366)	650 (530)	.25
Ethnicity, % of participants			
White	73.9	61.9	.34
Hispanic	21.7	38.1	
Other	4.3	0.0	
Female sex, No. (%) of participants	9 (39.1)	12 (57.1)	.37
MMSE score, mean (SD)	27.9 (2.0)	29.2 (0.9)	.010
CDR score,[c] No. (%) of participants			.003
0	9 (40.9)	16 (76.2)	
0.5	2 (9.1)	5 (23.8)	
1	9 (40.9)	0 (0.0)	
2	2 (9.1)	0 (0.0)	
Clinical diagnosis, No. (%) of participants			.02
Normal	5 (21.7)	6 (28.6)	
Mild cognitive impairment	7 (30.4)	13 (61.9)	
Dementia	11 (47.8)	2 (9.5)	
z Score, mean (SD)			
Psychomotor speed	−0.58 (1.1)	−0.11 (0.74)	.11
Attention	−0.64 (0.95)	0.00 (0.83)	.03
Memory	−0.51 (0.91)	−0.14 (0.79)	.16
Visuospatial function	−0.44 (1.3)	0.10 (0.59)	.08
Executive function	−0.53 (0.90)	−0.07 (0.63)	.06

Abbreviations: CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; UPDRS-III, Unified Parkinson Disease Rating Scale Part III.

[a] Four noncarriers completed only portions of the neuropsychological examination.

[b] Four homozygotes and 17 compound heterozygotes who carry 2 mutations in *PARKIN*.

[c] One noncarrier did not receive a CDR score.

highly correlated with lower UPDRS-III scores (psychomotor speed: $r = -0.503$, $P = .001$; attention: $r = -0.541$, $P < .001$; memory: $r = -0.597$, $P < .001$; visuospatial: $r = -0.635$, $P < .001$; and executive function: $r = -0.468$, $P = .002$). Therefore, when each of the cognitive domains was included in the adjusted models with UPDRS-III score as the outcome, the association between *PARKIN* mutation status and UPDRS-III score was not significant. Similarly, when the UPDRS-III score was included in the adjusted models, with each cognitive performance domain as the outcome, the association between *PARKIN* mutation status and performance in each cognitive domain was not significant.

Discussion

Among patients with EOPD, we have demonstrated that homozygotes and compound heterozygotes who carry *PARKIN* mutations and have a long disease duration perform better than noncarriers on tests of attention, memory, and visuospatial cognitive domains and on motor examinations during the "on" state. Motor and cognitive performances were very strongly correlated, as expected. These findings are consistent with the milder motor PD previously reported in homozygotes and compound heterozygotes who carry *PARKIN* mutations compared with noncarriers in cross-sectional analyses[17] and with previously reported clinical observations that dementia is rare among homozygotes and compound heterozygotes who carry *PARKIN* mutations.[1,18-21] However, the differences in cognitive performance identified in the present study contrast with previous findings (including those from our own cohort) in that no significant differences in neuropsychological performance between H/CH carriers and noncarriers were shown.[2,3] The possible explanations for the discrepancy are that H/CH carriers are less likely to develop the cognitive impairment and dementia that often occurs as PD advances, and that the pathology in *PARKIN*-associated PD remains circumscribed to the substantia nigra, even as the disease progresses. Autopsy data also support this hypothesis. Brain autopsies from homozygotes and compound heterozygotes who carry *PARKIN* mutations demonstrate nigral atrophy, but without neurodegenerative pathology in the cortex; neither Lewy bodies nor Alzheimer disease neuropathology is present in these brains, with rare exceptions.[22,23] In contrast, Lewy bodies and Alzheimer disease–like changes are the most common findings in autopsies of patients with PD dementia.[24] We have also previously reported that homozygotes and compound heterozygotes who carry *PARKIN* mutations are less likely than other

Table 2. Linear Regression Models Testing the Association Between *PARKIN* Mutation Status and Cognitive Domain Performance Among Patients With Early-Onset Parkinson Disease of Long Duration (>14 Years)[a]

	Noncarriers vs Carriers	
Performance	β (95% CI)	*P* Value
Unified Parkinson Disease Rating Scale	4.70 (0.89-8.50)	.02
Psychomotor speed	−0.32 (−0.75 to 0.12)	.15
Attention	−0.42 (−0.79 to −0.05)	.03
Memory	−0.36 (−0.67 to −0.05)	.03
Visuospatial function	−0.48 (−0.90 to −0.07)	.02
Executive function	−0.28 (−0.58 to 0.01)	.06

[a] Models are adjusted for age, sex, disease duration, education, levodopa equivalent daily dose, and language in which the tests were performed (English or Spanish). The analyses were performed on 4 homozygotes and 17 compound heterozygotes who carry 2 mutations in *PARKIN* (ie, 21 carriers) and 23 noncarriers of mutations in *PARKIN*, *PINK-1*, *DJ-1*, *LRRK2*, or *GBA*. However, 4 noncarriers completed only portions of the neuropsychological examination.

patients with EOPD to manifest hyposmia.[25] These clinical findings, as well as the autopsy data, suggest a "purer dopaminergic deficit" in *PARKIN*-associated PD.

Our findings may have important implications for genetic testing and for the counseling of homozygotes and compound heterozygotes who carry *PARKIN* mutations. Recent studies have demonstrated that patients with PD are interested in genetic testing results, but they may not fully understand the implications of these results or the benefits of genetic counseling.[26-28] Considering that homozygotes and compound heterozygotes who carry *PARKIN* mutations develop PD at a younger age than noncarriers, they may be concerned about their risk for dementia and their long-term ability to work. These H/CH carriers may benefit from the assurance that they have a lower risk for dementia than patients with idiopathic PD.

The major strengths of our study include the size of our cohort, given that it represents the largest sample size of mutation carriers with long disease duration reported, to date, and the comprehensive neuropsychological battery used. Our noncarrier EOPD group is likely an appropriate comparison group, having been screened for mutations in *PARKIN*, *GBA*, *LRRK2*, *SNCA*, *PINK-1*, and *DJ-1*.[5] We previously showed, using the same battery and a noncarrier control group, that noncarriers with EOPD perform better than *GBA* mutation carriers.[11] A significant limitation of our study is its cross-sectional design. In spite of our efforts to match the genetic groups by including only patients with EOPD of long duration, noncarriers were older than H/CH carriers, and the H/CH carriers had a longer duration of disease than did the noncarriers, although we did adjust for this in the analyses. Future studies that investigate the effects of disease duration on cognitive and motor function, including those with longitudinal follow-up, will help confirm our observation that *PARKIN*-associated PD may progress more slowly than idiopathic PD.

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