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Neuropsychological profile of parkin mutation carriers with and without Parkinson disease: the CORE-PD study

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Abstract

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Background—The cognitive profile of early onset Parkinson's disease (EOPD) has not been clearly defined. Mutations in the parkin gene are the most common genetic risk factor for EOPD and may offer information about the neuropsychological pattern of performance in both symptomatic and asymptomatic mutation carriers.

Methods—EOPD probands and their first-degree relatives who did not have Parkinson's disease (PD) were genotyped for mutations in the parkin gene and administered a comprehensive neuropsychological battery. Performance was compared between EOPD probands with (N=43) and without (N=52) parkin mutations. The same neuropsychological battery was administered to 217 first-degree relatives to assess neuropsychological function in individuals who carry parkin mutations but do not have PD.

Results—No significant differences in neuropsychological test performance were found between parkin carrier and non-carrier probands. Performance also did not differ between EOPD non-carriers and carrier subgroups (i.e. heterozygotes, compound heterozygotes/homozygotes). Similarly, no differences were found among unaffected family members across genotypes. Mean neuropsychological test performance was within normal range in all probands and relatives.

Conclusions—Carriers of parkin mutations, whether or not they have PD, do not perform differently on neuropsychological measures as compared to non-carriers. The cognitive functioning of parkin carriers over time warrants further study.

Keywords

Parkinson's disease; genetics; neuropsychological assessment; genotype; PARK2; parkin mutation

Introduction

The frontal-subcortical pattern of cognitive deficits associated with Parkinson's disease, which is most often diagnosed after age 50, is well-documented. In contrast, the cognitive profile of early-onset Parkinson's disease (EOPD), defined by age at onset of 50 or younger (Hedrich et al., 2001; Lucking et al., 2000) and affecting up to 10% of all PD patients (Schrag & Schott, 2006) is not well defined. Parkin mutations are a common cause of parkinsonism and are the most common mutations associated with EOPD, particularly among those < 30 years of age (Hedrich et al., 2001; Lucking et al., 2000; Schrag & Schott 2006; Wang et al., 2008), although mutations and variants in other genes have also been found in these cases including leucine-rich repeat kinase-2 (*LRRK2*) and glucocerebrosidase (*GBA*).

Mutations in the parkin gene have been identified in homozygous states, i.e. when the same mutation is inherited from each parent; compound heterozygous states, i.e. when different mutations in the same gene are inherited from each parent; and heterozygous states, i.e. when a single mutation is inherited from one parent. The likelihood that one parkin mutation may predispose to later disease onset is supported by studies that have identified heterozygous mutations in patients with Parkinson's disease (Clark et al., 2006; Foroud et al., 2003; Lesage et al. 2008; Moro et al., 2008; Pramstaller et al., 2005) and PD onset is earlier in carriers of two mutations (homozygous or compound heterozygous) when compared to carriers of one mutation (heterozygous) suggesting that a dosage effect may exist. However, the pathogenicity of heterozygous mutations is debated (Lincoln et al., 2003; Oliveira et al., 2003).

Studies of the cognitive profile of EOPD and the role of parkin on cognitive function are limited. Early animal models of parkin deficiency reported decreased exploratory behavior in parkin-deficient mice (Zhu et al., 2007) but another study did not observe any behavioral

differences (Perez & Palmiter, 2005). In a family-based study, no differences were found on Mini-Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) performance between 101 parkin carriers with one or two mutations identified and 85 non-carriers (Lucking et al., 2000). Khan et al (2003) reported a mean MMSE score of 28/30 in their study of 24 EOPD patients with parkin mutations. Given that two patients from their sample had at least 45 years of parkin-related PD, these normal scores on the MMSE were interpreted as suggesting that parkin mutations do not affect brain areas implicated in cognitive dysfunction. We did not detect any difference in MMSE performance when 43 parkin carriers were compared to 596 controls (Alcalay et al., 2010).

To date, only one study has systematically compared the cognitive performance of EOPD parkin carriers and non-carriers with an extensive neuropsychological battery (Lohmann et al., 2009). In that study EOPD patients who were parkin homozygotes or compound heterozygotes (n=21) did not differ in cognitive performance from parkin non-carrier (n=23) s, nor from unaffected siblings with parkin mutations (n=9), on any of the neuropsychological measures assessed. Four patients with parkin mutations and one healthy heterozygous parkin carrier scored within the abnormal range on a general measure used as part of the neuropsychological evaluation (i.e. Mattis Dementia Rating Scale) but comparisons of the other tests scores to normative data were not presented, making it difficult to assume normal cognitive performance for these patients or even for their unaffected siblings.

Here we examined the possible effects of parkin mutations on cognitive functioning using the largest sample of EOPD patients assembled to date who were recruited based on an age at onset of motor signs ≥ 50 years, independently of family history of PD. We compared the neuropsychological performance of EOPD parkin carriers to EOPD non-carriers in this way, among EOPD patients, parkin carriers represented cases while non-carriers were used as controls. We hypothesized that EOPD patients who were carriers of parkin mutations would exhibit more cognitive impairment compared to EOPD non-carriers and that the pattern of impairment would be consistent with that observed in Parkinson's disease; specifically, we expected to find subtle frontal-subcortical deficits. In addition, to evaluate the role of parkin mutation status on cognitive function independently of PD diagnosis, we compared the neuropsychological profile of family members who were non-carriers of parkin mutations to that of family members who carried mutations but were not diagnosed with PD. We hypothesized that mutation carriers would have subtle cognitive impairment when compared to non-carriers; therefore examining the cognitive profile of unaffected family members may assist in identifying individuals at risk for the development of PD and provide information about whether cognitive changes represent premotor manifestations of EOPD.

A secondary aim of the present study was to examine the cognitive profile of a large series of EOPD patients given that the literature on the neuropsychological performance of this group is limited. The few previous studies that have reported on the neuropsychological performance of EOPD patients have been constrained by limited test batteries or small sample sizes.

Methods

Subjects

Study design and statistical analysis—Probands, i.e. cases with EOPD defined by an age at onset of PD ≥ 50 years, were recruited at Columbia University from 1998 to 2003 through the Genetic Epidemiology of PD study (GEPD) (n=247), using methods previously described (Marder et al., 2003a). Additional probands with EOPD were recruited from 13 centers participating in the Consortium of Risk for Early-onset PD (CORE-PD) study from

2004 through 2009 (n=709) (Marder et al, 2009). Institutional review boards at all participating sites approved the protocols and consent procedures. To ensure that an accurate history could be obtained from each subject, only patients scoring ≥ 24 on the MMSE were included. Inclusion criteria in both studies required the diagnosis of PD based on the UK brain bank criteria (Hughes, Daniel, Kilford, & Lees, 1992), and an age at onset <50 years. In addition to the MMSE, Part I of the CORE-PD assessment included demographic information, a Unified Parkinson's Disease rating scale (UPDRS) (Fahn & Elton, 1987), a validated family history interview (Marder et al, 2003b) and a blood sample for DNA. Part II of the CORE-PD study focused on probands with parkin mutations and their first-degree family members (parents, siblings and children) who were 18 years and older. Families were further expanded by collecting the same information on first-degree relatives of each newly discovered family member found to have PD or carry a parkin mutation (Marder et al, 2009). Cutoff scores for MMSE were not applied to family members. These participants were further evaluated with a detailed examination including a neuropsychological battery and a psychiatric evaluation, including the Beck Depression Inventory-II (BDI II; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). In addition to an in-person evaluation, a videotaped assessment of the UPDRS was evaluated by a movement disorders specialist (EDL).

Molecular genetic analyses—We have previously described the methods used to detect mutations in the parkin gene in the 247 cases recruited in GEPD (Wang et al., 2008). In CORE-PD, we screened 709 samples obtained from PD probands for point mutations using denaturing high performance liquid chromatography and a parkin genotyping array (Clark et al., 2007) and for copy number variation (exon deletions and duplications) using semi-quantitative multiplex polymerase chain reaction (Clark et al., 2006). The genotyping array was used to analyze amplicons in DNA samples with abnormal elution profiles and has excellent sensitivity and specificity for detection of sequence variants when compared to the gold standard of sequencing (Clark et al., 2007). In the present study, parkin mutations were assessed by sequencing in 26 probands initially recruited in GEPD. Mutations in the other 69 probands in CORE-PD who had Part II evaluations were assessed using denaturing high performance liquid chromatography and the genotyping array and multiplex polymerase chain reaction. DNA samples from all 204 relatives were analyzed using the genotyping array and semi-quantitative multiplex polymerase chain reaction. The genotyping array also included mutations in other genes associated with PD, including the Leucine-rich repeat kinase 2 (*LRRK2*) G2019S mutation and the glucocerebrosidase (*GBA*) N370S and L444P mutations (Clark et al., 2007). Participants with mutations in these genes were excluded, as described below.

Neuropsychological Evaluation—The neuropsychological battery was composed of measures corresponding to five cognitive domains selected based on previous research assessing predictors of cognitive decline in PD (Muslimovic, Post, Speelman, DeHaan, & Schmand, 2005; Muslimovic, Post, Speelman, DeHaan, & Schmand, 2009). These domains included psychomotor speed, attention, memory, visuospatial function, and executive function. With the exception of verbal fluency tests, additional tests of language function were not included in the battery because language dysfunction is rarely reported in non-demented PD patients (Levin, Llabre, & Weiner, 1989; Lewis, Lapointe, & Murdoch., 1998).

Psychomotor speed was assessed with the Trail Making Test, Part A (TMT-A)(Reitan & Wolfson, 1992; Spreen & Strauss, 1991) and Stroop Color Word Test Part A (word reading) and Part B (color naming) trials (Golden, 1978). Attention was examined with the Trail Making Test Part B (TMT-B)(Reitan & Wolfson, 1992) and Stroop Color Word Test Part C (color word trial) (Golden, 1978). Memory was assessed with the California Verbal

Learning Test-II (CVLT-II; Woods, Delis, Scott, Kramer, & Holdnack, 2006) (Artoli i Fortuny, Romo, Heaton, & Pardee, 1991), Wechsler Memory Scale-R Visual Reproduction subtest (WMS-R Visual Reproduction)(Wechsler, 1987), and Benton Visual Retention Test-Revised Delayed Recall trial (BVRT; Benton, 1974). Visuospatial function was examined with the Benton Visual Retention Test-Revised, Matching Trial (BVRT; Benton, 1974) and the Benton Facial Recognition Test (BFRT; Benton, Sivan, Hamsher, Varney, & Spreen, 1994). Executive function was assessed with the Controlled Oral Word Association Test (COWAT) (Benton et al, 1994), Category fluency (animals) (Luteijn & Barelds, 2004; Spreen & Strauss 1991) and CVLT-II Recognition Errors (False Positives). MMSE scores were obtained on all participants as part of the screening process for proband recruitment and these scores were included in data collection and analyses as well. The Digit Span subtest from the WAIS-III was added to the battery after data collection had begun; therefore, limited data are available for this test and it was subsequently not included in the domain scores.

Practical considerations demanded that the test battery be able to be administered in participants' homes. Therefore, testing was designed to be as brief as possible and able to be completed by patients with motor impairment. The battery was comprised of measures that could be administered in English or Spanish. For the purposes of Spanish test administration, all items and instructions for the tests were translated into Spanish and then translated back again to ensure accuracy. Tests were administered in person, either in English or Spanish, by a bilingual psychometrician (LR) who received training on test administration and scoring by a neuropsychologist (EC). The psychometrician was not aware of the genetic status of the participants. All participants were maintained on their medications for neuropsychological testing. All test results were scored by the psychometrician and double-scored by a second psychometrician.

Statistical Analysis

General: Analyses were performed separately for the PD proband group and for first-degree relatives who were not diagnosed with PD. Twenty-three participants who were also carriers of *LRRK2* or *GBA* mutations irrespective of whether they had PD were excluded from the analyses to examine the effect of parkin mutation status independently. Individual neuropsychological test scores for all probands and their family members were transformed to create Z-scores using means and standard deviations of the entire sample which included all cases and their family members. Composite scores for each domain were computed by averaging the mean Z-scores from the individual tests comprising each domain.

To examine the cognitive functioning of subjects from a more clinically relevant perspective, raw scores from individual neuropsychological tests were standardized using age and education-based norms (Appendix 1). Impaired performance on a test was defined as a score that fell at least 1.5 standard deviations below the mean of the normative sample (i.e. from published norms).

Probands—Demographic and disease characteristics, individual test scores and domain scores of 43 EOPD probands who carried a parkin mutation (heterozygote, homozygote, compound heterozygote) and a sample of EOPD non-carriers (n=52) were compared using chi square tests with Kruskal-Wallis post-hoc tests for categorical variables and Student's t-test for continuous variables. Mean domain scores were also compared by gender. Logistic regression models were constructed to predict group membership (dichotomous outcome = parkin carriers vs. non carriers), with domain scores, age, education, gender, BDI-II score, side of disease onset, age at onset and initial PD symptom used as covariates. Educational level was truncated at 20 years. Given the high variability in the initial symptom

presentation of PD, we dichotomized this variable to either the most common presenting symptom (rest tremor) vs. others (e.g. gait instability, micrographia, etc.). Any covariates associated with group membership at $p < 0.10$ in bivariate analyses were included in subsequent multivariate regression models. In separate analyses, proband parkin-carriers were further divided into two groups: those with a single mutation (heterozygotes) and those with two mutations (compound heterozygotes and homozygotes). The domain scores and individual test scores (both raw and standardized) of these two groups were compared to those of non-carrier probands with one way analysis of variance (ANOVA) and Tukey post-hoc tests to assess the gene-dosage effect (one vs. two mutations) on cognitive function. These analyses were conducted with and without Spanish speakers ($n = 14$) to examine the possible effect of the language testing was administered in.

First-Degree Relatives—The demographics and cognitive performance of first-degree relatives were compared similarly to that of probands; i.e. two analyses were conducted comparing the performance (i.e. domain scores) of parkin carriers to that of noncarriers and also comparing the performance of family members who were either carriers of one mutation, two mutations (compound heterozygotes only, as there were no homozygote family members) or non-carriers. A backwards-stepwise regression with Generalized Estimating Equations (GEE) (Zeger & Liang, 1986) was used to evaluate the effect of family relationship on test (domain) performance. This approach takes into account the possibility that characteristics among family members are correlated. Finally, this same GEE approach was used to compare the cognitive performance of probands with PD (cases) and their non-affected siblings (controls).

Results

Probands

Demographics—After excluding probands with other known mutations including GBA ($n=8$) or *LRRK2* ($n=2$), 95 EOPD patients (54 men, 41 women) were evaluated, including 52 non-carriers, 23 parkin heterozygotes, and 20 cases with two parkin mutations (16 compound heterozygotes and 4 homozygotes). Demographic and clinical characteristics of the proband group are shown in Table 1.

When the sample was dichotomized (parkin carriers versus non-carriers) the groups were similar with regard to demographics and disease characteristics, except for age at onset which was younger in the parkin carrier group. When the proband group was divided into three groups, non-carriers, heterozygotes and carriers of two mutations, again, only age-at-onset was significantly different among the groups (Table 1).

Neuropsychological Performance—Performance on cognitive domains was similar among the mutation groups (Table 2). No significant differences were found on either raw or standardized test scores, whether two or three groups were compared. In the logistic regression model where parkin status was the dependent variable, no cognitive domain was associated with mutation status, either in a univariate model nor when data was stratified by demographic or disease-related variables including age, education, gender, side of disease onset, age at onset, initial PD symptom, or BDI-II score. The language used for test administration (English versus Spanish) did not change these results.

Individual test scores in both raw and standardized form are provided in table form (Table 3) for descriptive purposes and provide a reference for the pattern of mean scores seen on this comprehensive battery. Table 3 can be found as an online supplement. Probands were not impaired, i.e. did not score ≥ 1.5 SD on any measure when mean standardized scores calculated from normative data were examined for non-carriers and carrier groups.

First-Degree Relatives

Demographics—We studied 217 family members (39 parents, 101 siblings and 77 children) including 146 non-carriers (22 parents, 77 siblings, 47 children), 65 heterozygotes (16 parents, 21 siblings, 28 children), and 6 compound heterozygous (1 parent, 3 siblings, 2 children; in four families), after excluding family members with PD diagnoses ($n=8$, all of whom were siblings) or carriers of other genetic mutations (3 *LRRK2* and 10 GBA mutation carriers) (Table 4).

Neuropsychological Performance—Whether two (parkin mutation carrier vs. non-carrier) or three groups (heterozygotes, compound heterozygotes, wild type) were compared using one way ANOVA and Tukey post-hoc tests, no significant differences were found for the five cognitive domains (Table 5).

No covariates emerged in the backward step-wise regression approach and domain scores were not associated with carrier status outcome. Individual test scores including raw and standardized scores are provided for descriptive purposes in Table 6, which is available as an online supplement. None of the mean standardized scores for individual tests fell 1.5 SDs below the normative mean for relatives.

Given our negative findings we performed a power analysis using PS2 software (version 3.0.2) to determine the detectable difference in domain score for each genetic group (heterozygotes, compound heterozygotes/homozygotes) compared to non-carriers. This study had 80% power to detect a large difference (.76 SD) among proband groups (compound heterozygotes/homozygotes, heterozygotes, and non-carriers) and a medium effect size among family members (heterozygotes vs. non-carriers).

We further tested whether our battery was sensitive for PD-related cognitive changes. When the mean domain scores of probands with PD were compared to those of their siblings without PD ($n=101$), probands were found to perform lower within the domains of speed ($p < .001$) and attention ($p < .001$), using a backwards-stepwise regression with GEE after adjusting for sex, age and education.

Discussion

Mutations in the parkin gene were recognized over a decade ago as a genetic cause of EOPD (Kitada et al., 1998; Periquet et al., 2003). Using the largest systematically collected sample of EOPD cases to date (Marder et al, 2009) this study examined the possible association between parkin mutation status and cognitive function by assessing the neuropsychological performance of EOPD patients as well as that of their unaffected first-degree relatives. Consistent with previous studies reporting normal cognitive function in parkin-carrier EOPD patients (Khan et al., 2003; Khan et al., 2005; van Nuenen et al. 2009) we found no significant differences in neuropsychological test performance between parkin carrier and non-carrier probands, even when examining the possible effects of demographic and disease-related factors including age, education, gender, side of disease onset, age at onset, initial PD symptom, and BDI-II score. We did not find that parkin mutation status confers cognitive vulnerability on any subgroup, including gender, side of onset and initial presenting symptom; however, our study was not powered for these subanalyses. Furthermore, performance between non-carriers and carrier subgroups, (i.e. heterozygotes, compound heterozygotes/homozygotes) did not differ, implying that there is no gene-dosage effect on cognitive functioning. It is important to note that our sample included only non-demented probands, a limitation which may have affected our ability to detect cognitive differences among probands with and without mutations.

When we tested our hypothesis that neuropsychological assessment may detect populations at risk for PD among family members with parkin mutations, we found no differences in cognitive functioning in unaffected first-degree relatives across genotypes, suggesting that cognitive changes may not represent premotor manifestations in parkin carriers at risk for the development of PD. The fact that unaffected relatives with parkin mutations did not exhibit impaired performance on any mean test score suggests that their genetic status does not affect their cognitive functioning on tests used in the present battery.

Our null findings, i.e. that parkin carrier and non-carrier probands did not differ in neuropsychological test performance and that unaffected parkin-carriers did not exhibit preclinical cognitive changes or impairment that precedes motor impairment, are strengthened by our use of a comprehensive neuropsychological battery as well as our use of a very large sample of EOPD patients who were recruited based on of motor signs as opposed to family history of PD status. The negative findings in this study suggest that either there is no phenotypic difference among the mutation groups or that differences in cognitive function were too subtle to be detected in our sample using this battery.

This study had limitations. First, in spite of its large sample size of EOPD cases, the smaller number of mutation carriers found allowed us to detect only a large effect in probands and a moderate effect in family members. Second, the neuropsychological battery used may not have been sensitive enough to capture subtle differences. As previously described, we were limited by our need for a brief test battery that could be administered to a diverse population (e.g. patients with motor impairments, Spanish speakers) in their homes.

Neuropsychological test data was analyzed as domain scores so as to reduce the data, and as individual test scores to avoid the loss of data that may occur with the use of pre-established domains. The categorization of tests within specific cognitive domains often appears arbitrary, however in devising our domain scores we attempted to replicate the domains used by Muslimovic et al (2003, 2009) in their previous studies that assessed predictors of cognitive decline in PD. In this way, data from the Trail Making Test and Stroop were categorized as tests of psychomotor speed (TMT Part A, Stroop color and word reading trials) and attention (TMT Part B, Stroop color-word trial). The authors also included fluency tasks within the domain of executive functioning (as opposed to language measures) and so this methodology was used in the present study. Additional support for the use of fluency tasks as executive measures is provided by the Dujardin, Duhamel, Becquet, Grunberg, Defebvre, & Destee (1999) study that found that the number of perseverative responses on phonemic fluency tasks differentiated first-degree relatives of PD patients from healthy controls.

Restricting our proband sample to those with MMSE scores > 23 may have limited the likelihood of identifying cognitive deficits; however, this limitation does not apply to the family members' data, since we did not restrict recruitment of unaffected relatives based on MMSE performance. Finally, our cross-sectional design precludes follow-up information that would allow us to examine cognitive change over time. Our use of normative data was reported so as to provide a clinically-relevant illustration of the cognitive performance of EOPD patients. When we compared probands' mean scores on individual test measures with normative data, none of the genetic groups exhibited impaired performance, defined as a mean score more than 1.5 standard deviations below the mean of age and education norms, on any measure. In fact, mean test scores did not fall below even one standard deviation, reflecting performance within normal limits for the proband group. As such, we can assume in terms of the actual observed values that this group is cognitively normal. Since cognitive impairment is frequent in PD, long term follow up of EOPD patients will assist in determining whether the rate of cognitive impairment differs between mutation groups.

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Table 1

Clinical and demographic characteristics of probands by parkin carrier status

	Total mean (SD), range N=95	Non- Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes/ Homozygotes) N=20	P value
Age	51.3 (9.1) 29 - 72	52.1 (8.2)	49.9 (8.2)	50.6 (12.4)	.58
Age at onset	37.9 (9.6) 7 - 50	42.1 (5.8) ^a	36.6 (10.5) ^b	28.4 (9.8) ^c	<.001
Highest grade (truncated at 20 years)	15.1 (2.9) 6 - 20	15.6 (3.0)	15.2 (2.4)	14.0 (3.0)	.10
UPDRS-III	19.6 (7.5) 2 - 51	20.1 (7.7)	19.6 (7.6)	18.4 (7.1)	.67
BDI-II Score (0-63)	10.0 (8.0) 0 - 33	10.4 (8.6)	9.9 (8.1)	9.11 (6.5)	.84
Race (Caucasian/Black/ Hispanic/Other)	76/1/14/4	45/1/4/2	17/0/4/2	14/0/6/0	
Gender (Male/Female)	54/41	31/21	13/10	10/10	.76
*Side symptoms began (Right/Left/ no asymmetry) n=50	16/24/10	8/14/6	4/6/3	4/4/1	.90
*First symptom = rest tremor? (No/Yes) n=76	44/32	26/17	12/6	6/9	.26
Medication (Levodopa- carbidopa/Dopamine agonist)	60/41	34/25	14/8	12/8	.70

Values are means +/- standard deviations. Analyses reflect differences at the .001 level for comparison of adjacent groups.

Values with different superscript letters reflect significant group differences on *post-hoc* testing, i.e. age at onset was significantly different in each group.

* This data was not collected within the GEPD study, resulting in a reduced n

Table 2

Composite domain scores of probands (reported as Z-scores) by parkin carrier status

Neuropsychological Domain	Total N=95	Non-Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes) N=20	P value
Psychomotor speed (Z-score)	-.38 (.69)	-.46 (.99)	-.17 (.55)	-.42 (.93)	.41
Attention (Z-score)	-.31 (.77)	-.29 (.76)	-.36 (.56)	-.29 (1.02)	.94
Memory (Z-score)	-.16 (.85)	-.17 (.95)	-.01 (.64)	-.32 (.82)	.50
Visuospatial function (Z-score)	-.12 (.67)	-.11 (.72)	-.06 (.52)	-.20 (.70)	.78
Executive function (Z-score)	-.14 (.87)	-.19 (.94)	.12 (.72)	-.31 (.81)	.22

Values are means +/- standard deviations. Analyses reflect comparisons across three groups on *post-hoc* testing.

Table 3
Individual neuropsychological test scores of probands by parkin carrier status (raw and standardized scores)

Test	Total N = 95	Non-Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes/ Homozygotes) N=20	P value
Psychomotor Speed					
Trail Making Test, Part A raw score (sec) range	44.17 (32.47) 19 - 240	48.12 (34.45) 19 - 240	38.00 (13.27) 20 - 72	41.00 (41.56) 19 - 205	.41
Trail Making Test, Part A percentile score range	31.16 (28.21) <1 - 97	24.86 (25.47) ^b <1 - 86	32.50 (30.37) ^{a b} <1 - 97	46.00 (28.05) ^a 1 - 92	.01
Stroop Test Word Reading raw score range	84.88 (18.03) 30 - 126	84.44 (19.70) 30 - 126	89.04 (12.52) 65 - 111	81.25 (18.72) 49 - 115	.36
Stroop Test Word Reading percentile score range	28.17 (21.31) <1 - 90	28.90 (22.18) <1 - 90	30.56 (19.28) 3 - 69	23.51 (21.55) <1 - 63	.52
Stroop Test Color Naming raw score range	60.12 (13.98) 13 - 96	58.84 (15.06) 13 - 85	62.96 (12.62) 33 - 82	60.10 (12.73) 40 - 96	.50
Stroop Test Color Naming percentile score range	22.70 (21.14) <1 - 87	22.36 (21.03) <1 - 72	25.74 (22.25) <1 - 67	20.05 (20.80) 2 - 87	.67
Attention					
Trail Making Test, Part B raw score (sec) range	99.09 (52.52) 30 - 240	98.47 (47.89) 33 - 220	99.87 (43.00) 36 - 201	99.70 (72.60) 30 - 240	.99
Trail Making Test, Part B percentile score range	35.65 (26.97) <1 - 89	34.33 (24.94) <1 - 84	31.22 (24.87) <1 - 80	44.00 (33.08) <1 - 89	.26
Stroop Color Word raw score range	34.19 (11.01) 10 - 57	34.14 (12.03) 10 - 56	33.52 (8.43) 20 - 50	35.10 (11.32) 15 - 57	.89
Stroop Color Word percentile score range	34.70 (28.09) 20 - 94	35.30 (29.90) <1 - 94	30.47 (24.89) 1 - 83	38.04 (27.53) <1 - 89	.66
Memory					
CVLT Total Recall	43.74 (11.31)	44.14 (11.76)	46.64 (11.58)	39.55 (8.82)	.11

Test	Total N = 95	Non-Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes/ Homozygotes) N=20	P value
(trials 1-5) raw score <i>Range</i>	17 - 71	17 - 64	31 - 71	26 - 55	
CVLT Total Recall (trials 1-5) percentile score <i>range</i>	45.78 (12.16) 1 - 71	47.18 (12.50) 1 - 65	45.19 (13.76) 2.2 - 71.0	42.77 (8.50) 26.0 - 57.0	.41
CVLT Long Delayed Free Recall raw score <i>range</i>	9.41 (3.81) 0 - 16	9.24 (4.34) 0 - 16	10.50 (2.73) 6 - 16	8.65 (3.23) 4 - 14	.26
CVLT Long Delayed Free Recall Z score <i>range</i>	-.01 (1.11) -3.50 - 2.30	-.02 (1.23) -3.50 - 2.00	.20 (.96) -1.50 - 2.30	-.29 (.94) -2.20 - 1.50	.47
CVLT Delayed Recog Total Hits raw score <i>range</i>	14.12 (2.12) 4 - 16	14.16 (2.18) 4 - 16	14.32 (1.83) 11 - 16	13.79 (2.34) 8 - 16	.72
CVLT Delayed Recog Total Hits Z score range	-.02 (.96) -5.00 - 1.00	.02 (1.05) -5.00 - 1.00	.10 (.63) -1.50 - 1.0	-.25 (1.01) -3.50 - .50	.54
WMS-R Visual Repro I raw score <i>range</i>	29.27 (7.83) 0 - 40	30.12 (8.28) 0 - 40	29.57 (5.44) 17 - 38	26.75 (8.72) 9 - 58	.26
WMS-R Visual Repro I percentile score <i>range</i>	52.26 (31.09) 1 - 98	58.30 (31.54) 1 - 98	46.82 (28.03) 5 - 98	42.80 (31.17) 1 - 94	.10
WMS-R Visual Repro II raw score <i>range</i>	24.88 (9.69) 0 - 38	25.62 (9.59) 0 - 38	25.43 (9.52) 4 - 37	22.35 (10.18) 0 - 36	.42
WMS-R Visual Repro II percentile score <i>range</i>	48.41 (30.31) 1 - 97	50.88 (29.37) 1 - 97	48.30 (31.21) 1 - 95	42.10 (32.32) 1 - 94	.55
BVRT Recognition subtest raw score <i>range</i>	8.67 (1.43) 2 - 10	8.56 (1.5) 2 - 10	8.74 (0.96) 7 - 10	8.90 (1.51) 5 - 10	.64
Visuospatial Function					
BVRT Matching subtest raw score <i>range</i>	9.75 (0.82) 4 - 10	9.73 (0.97) 4 - 10	9.83 (0.49) 8 - 10	9.70 (0.73) 8 - 10	.86
Facial Recognition Total raw score	22.18 (2.84) 15 - 39	22.44 (3.15) 16 - 39	21.86 (2.76) 15 - 27	21.85 (2.00) 18 - 25	.61

Test	Total N = 95	Non-Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes/ Homozygotes) N=20	P value
<i>range</i>					
Facial Recognition Total T score <i>range</i>	45.36 (4.17) 33 - 54	45.54 (3.82) 37 - 52	45.09 (5.11) 33 - 54	45.20 (4.12) 37 - 51	.90
Executive Function					
COWAT Total Raw score <i>range</i>	38.14 (12.87) 9 - 63	37.42 (13.96) 9 - 63	40.57 (10.11) 22 - 62	37.20 (13.00) 12 - 57	.58
COWAT Total percentile score <i>range</i>	57.01 (33.26) 1 - 99	55.65 (34.71) 1 - 99	62.48 (29.72) 8 - 99	54.25 (34.15) 1 - 97	.66
Category Fluency Total raw score <i>range</i>	18.61 (5.47) 2 - 30	18.41 (5.94) 2 - 30	19.39 (4.45) 12 - 29	18.20 (5.45) 9 - 29	.72
Category Fluency Total percentile score <i>range</i>	32.81 (24.14) <1 - 88	34.67 (26.27) <1 - 88	29.69 (17.93) 6 - 85	31.66 (25.35) <1 - 84	.69
CVLT Delayed Recog False Positives raw score <i>range</i>	3.26 (3.54) 0 - 17	3.16 (3.12) ^{ab} 0 - 13	2.18 (3.48) ^a 0 - 16	4.79 (4.25) ^b 0 - 17	.05
CVLT Delayed Recog False Positives Z score <i>range</i>	60 (1.03) -1.50 - 4.50	.52 (.86) -.50 - 2.50	.70 (1.35) -.50 - 4.50	.71 (1.18) .76 -1.50 - 3.50	
Not included in domain scores					
MMSE <i>range</i>	28.95 (1.35) 24 - 30	28.85 (1.55) 24 - 30	29.04 (1.18) 27 - 30	29.10 (.96) 27 - 30	.72
Digit Span Forward* Total Correct <i>range</i>	9.17 (2.22) 3 - 12 n=45	9.63 (2.27) ^a 3 - 12 n=22	9.72 (1.84) ^a 7 - 12 n=12	7.83 (2.03) ^b 4 - 11 n=11	.04
Digit Span Forward* Length <i>range</i>	7.04 (1.29) 2 - 10	7.18 (1.36) ^{ab} 2 - 8	7.64 (1.02) ^a 6 - 10	6.25 (1.05) ^b 4 - 8	.02
Digit Span Backward* Total Correct <i>range</i>	6.20 (2.45) 2 - 11	6.54 (2.66) 2 - 11	6.72 (2.57) 3 - 10	5.08 (1.62) 2 - 8	.18

Test	Total N = 95	Non-Carriers N=52	Single mutation (Heterozygotes) N=23	Two mutations (Compound heterozygotes/ Homozygotes) N=20	P value
Digit Span Backward [*] Length range	4.73 (1.49) 2 - 7	4.86 (1.61) 2 - 7	5.18 (1.53) 3 - 7	4.08 (1.08) 2 - 6	.18

Values are means +/- standard deviations. Values with different superscript letters reflect significant differences across groups on *post-hoc* testing; a=highest score, b=lowest score.

For Trail Making Test, parts A and B and CVLT-II False Positives, low raw scores are indicative of better performance.

* Digit Span subtest was administered to a subset of subjects in each of the four groups specified above (total = 45; 22, 12, 11).

Table 4

Demographic characteristics of unaffected first-degree relatives by parkin carrier status

	Total N = 217	Non-Carriers N=146	Single mutation (Heterozygote s) N=65	Two mutations (Compound heterozygotes) N=6	P value
Relationship of subject					
Parent	39	22	16	1	
Sibling	101	77	21	3	
Child	77	47	28	2	
Age (total)	47.0(18.1) <i>18 - 95</i>	47.5 (18.1) ^a	47.2 (19.8) ^a	50.0 (24.2) ^b	<.001
Parent		72.5 (8.8)	70.2 (7.4)	76 (0)	
Sibling		52.3 (12.2)	51.8 (13.4)	45.6 (2.5)	
Child		28.6 (7.5)	29.6 (9.0)	24 (5.6)	
Highest Grade (truncated at 20 years)	14.3 (2.8) <i>0 - 20</i>	14.1 (3.0)	14.5 (2.5)	12.6 (1.9)	.11
Parent		13.3 (4.3)	14.6 (1.9)	11 (1.7)	
Sibling		13.9 (3.0)	15.5 (2.5)	13.0 (2.6)	
Child		15.0 (2.1)	14.1 (2.4)	13.0 (1.4)	
Race					
Caucasian	184	124	54	6	
Black	2	1	1	0	
Hispanic	27	20	7	0	
Other	4	1	3	0	
BDI-II Score (total)	4.9 (5.8) <i>0 - 27</i>	5.2 (6.1) ^a	3.7 (4.8) ^{ab}	10.0 (7.7) ^b	.03
Parent	5.5 (5.5)	5.2 (4.9)	5.9 (6.4)	5.5 (5.5)	.71
Sibling	5.4 (5.5)	6.0 (6.4) ^a	3.7 (4.4) ^a	14.3 (6.0) ^b	.02
Child	3.9 (5.5)	4.8 (6.3)	2.7 (3.9)	3.5 (4.9)	.63

Values are means $\pm$ standard deviations. Values with different superscript letters reflect significant group differences on *post-hoc* testing. Analyses reflect differences at the .001 level for comparison of adjacent groups. Values with different superscript letters reflect significant group differences on *post-hoc* testing.

Table 5

Composite domain scores of unaffected first-degree relatives (reported as Z-scores) by parkin carrier status

Neuropsychological Domain	Total N=217	Non-Carriers N=146	Single mutation (Heterozygotes) N=65	Two mutations (Compound heterozygotes/ Homozygotes) N=6	P value
Psychomotor speed (Z-score)	.14 (.68)	.13 (.71)	.15 (.64)	.41 (.57)	.67
Attention (Z-score)	.14 (.75)	.13 (.78)	.14 (.70)	.35 (.42)	.81
Memory (Z-score)	.08 (.69)	.05 (.72)	.11 (.65)	.40 (.28)	.50
Visuospatial function (Z-score)	.01 (.78)	-.00 (.78)	.04 (.83)	.03 (.10)	.90
Executive function (Z-score)	.05 (.64)	.03 (.66)	.12 (.62)	-.13 (.14)	.54

Values are means +/- standard deviations. Analyses reflect comparisons across three groups on *post-hoc* testing.

Table 6
Individual neuropsychological test scores of unaffected first-degree relatives by parkin carrier status (raw and standardized scores)

Test	Total N = 217	Non-Carriers N=146	Single mutation (Heterozygotes) N=65	Two mutations (Compound heterozygotes/ Homozygotes) N=6	P value
Psychomotor Speed					
Trail Making Test, Part A raw score (sec) range	32.77 (15.49) 14 - 105	32.87 (15.10) 16 - 100	33.00 (16.86) 14 - 105	27.00 (7.10) 18 - 37	.70
Trail Making Test, Part A percentile score range	44.55 (29.86) <1 - 93	43.87 (28.56) <1 - 92	45.00 (32.38) <1 - 93	58.52 (36.91) <1 - 89	.55
Stroop Test Word Reading raw score range	96.37 (16.00) 40 - 136	95.68 (16.77) 40 - 136	97.32 (14.19) 63 - 129	104.00 (15.57) 83 - 123	.44
Stroop Test Word Reading percentile score range	42.62 (23.77) <1 - 99	41.68 (23.49) <1 - 90	44.29 (24.50) 3 - 99	48.00 (25.58) 11 - 76	.67
Stroop Test Color Naming raw score range	67.77 (13.66) 14 - 100	67.63 (14.49) 14 - 100	67.89 (11.94) 42 - 84	70.00 (12.66) 52 - 87	.92
Stroop Test Color Naming percentile score range	33.65 (23.04) <1 - 99	33.58 (24.04) <1 - 99	33.75 (21.00) 2 - 77	34.20 (24.80) 4 - 69	.99
Attention					
Trail Making Test, Part B raw score (sec) range	73.51 (42.49) 27 - 284	73.23 (43.95) 27 - 284	74.37 (41.11) 30 - 245	70.60 (10.06) 55 - 81	.97
Trail Making Test, Part B percentile score range	50.95 (28.79) <1 - 99	51.06 (28.66) <1 - 99	50.68 (29.99) <1 - 94	51.00 (21.00) 16 - 70	.99
Stroop Color Word Raw score range	39.69 (12.63) 13 - 75	39.38 (12.63) 13 - 75	39.97 (10.33) 17 - 65	44.60 (9.07) 35 - 55	.61
Stroop Color Word percentile score range	46.85 (27.95) <1 - 99	46.14 (28.99) <1 - 99	47.83 (25.63) 2 - 99	54.40 (31.28) 16 - 88	.76
Memory CVLT Total Recall (trials 1-5) raw score	46.45 (10.30) 6 - 72	46.50 (10.18) 13 - 67	46.77 (9.81) 20 - 72	41.67 (17.5) 6 - 51	.50

Test	Total N = 217	Non-Carriers N=146	Single mutation (Heterozygotes) N=65	Two mutations (Compound heterozygotes/ Homozygotes) N=6	P value
<i>range</i>					
CVLT Total Recall (trials 1-5) percentile score <i>range</i>	47.27 (11.15) 1 - 74	47.40 (11.14) 1 - 74	47.40 (10.65) 1 - 71	43.00 (16.86) 10 - 57	.63
CVLT Long Delayed Free Recall raw score <i>range</i>	10.19 (3.15) 0 - 16	10.31 (2.84) 0 - 16	10.25 (3.11) 1 - 16	9.83 (5.26) 0 - 15	.91
CVLT Long Delayed Free Recall Z score <i>range</i>	-.06 (.96) -3.50 - 2.50	-.07 (.98) -3.50 - 2.50	-.04 (.90) -2.50 - 1.50	-.10 (1.38) -2.50 - 1.00	.98
CVLT Delayed Recog Total Hits raw score <i>range</i>	14.31 (2.04) 4 - 16	14.25 (2.05) 4 - 16	14.41 (2.02) 6 - 16	14.67 (2.33) 10 - 16	.80
CVLT Delayed Recog Total Hits Z score <i>range</i>	-.20 (.94) -5.00 - 1.50	-.22 (.92) -5.00 - 1.50	-.19 (1.03) -4.00 - 1.00	.10 (.54) -.50 - 1.00	.75
WMS-R Visual Repro I raw score <i>range</i>	31.36 (6.87) 2 - 41	31.17 (7.31) 2 - 41	31.70 (5.95) 8 - 40	32.40 (5.36) 27 - 41	.82
WMS-R Visual Repro I percentile score <i>range</i>	59.12 (28.84) 1 - 99	58.50 (30.14) 1 - 99	61.35 (25.64) 2 - 98	48.60 (32.05) 18 - 99	.57
WMS-R Visual Repro II raw score <i>range</i>	26.77 (9.07) 0 - 41	26.63 (9.42) 0 - 40	26.81 (8.47) 0 - 38	30.40 (6.87) 23 - 41	.66
WMS-R Visual Repro II percentile score <i>range</i>	53.43 (30.44) 1 - 99	52.66 (31.16) 1 - 99	55.12 (28.99) 1 - 97	53.80 (33.08) 12 - 99	.86
BVRT Recognition subtest raw score <i>range</i>	9.22 (1.05) 4 - 10	9.22 (1.09) 4 - 10	9.25 (.96) 6 - 10	9.00 (1.09) 7 - 10	.86
Visuospatial Function					
BVRT Matching subtest raw score <i>range</i>	9.82 (0.57) 6 - 10	9.82 (0.61) 6 - 10	9.80 (0.50) 7 - 10	10.00 (0.00) 10 - 10	.71
Facial Recognition Total raw score <i>range</i>	22.85 (4.78) 8 - 54	22.70 (4.46) 8 - 50	23.25 (5.59) 15 - 54	21.80 (0.83) 21 - 23	.66

Test	Total N = 217	Non-Carriers N=146	Single mutation (Heterozygotes) N=65	Two mutations (Compound heterozygotes/ Homozygotes) N=6	P value
Facial Recognition Total T score range	45.84 (5.31) 0 - 54	45.94 (4.46) 25 - 54	45.71 (6.99) 0 - 54	44.60 (1.67) 43 - 47	.83
Executive Function					
COWAT Total raw score range	37.55 (10.95) 11 - 73	37.66 (11.23) 11 - 73	37.54 (10.78) 18 - 68	34.40 (2.51) 32 - 38	.80
COWAT Total percentile score range	58.30 (28.19) 1 - 100	57.77 (28.48) 1 - 100	60.16 (28.42) 3 - 99	50.20 (16.14) 34 - 69	.69
Category Fluency Total raw score range	19.92 (4.40) 7 - 34	19.87 (4.38) 7 - 34	20.19 (4.55) 9 - 30	17.80 (2.77) 15 - 21	.49
Category Fluency Total percentile score range	33.59 (21.67) <1 - 97	33.40 (20.81) <1 - 97	35.67 (23.49) 3 - 92	12.40 (9.91) 3 - 26	.06
CVLT Delayed Recog False Positives raw score range	2.12 (2.48) 0 - 15	2.75 (2.62) 0 - 15	1.95 (2.14) 0 - 10	2.50 (2.58) 0 - 7	.78
CVLT Delayed Recog ¹ False Positives Z score range	.62 (.25) -1.50 - 4.00	.23 (.88) -1.50 - 4.00	.14 (.65) -.50 - 2.00	.62 (.25) .50 - 1.00	.48
Not included in domain scores					
MMSE range	29.03 (2.19) 12 - 30	29.12 (2.03) ^a 14 - 30	29.06 (1.53) ^a 22-30	26.67 (7.2) ^b 12 - 30	.02
Digit Span Forward Total Correct range	9.22 (2.03) 3 - 12 n=93	9.35 (2.19) 3 - 12 n=62	9.19 (1.62) 7 - 12 n=27	7.66 (2.30) 5 - 9 n=4	.37
Digit Span Forward Length range	7.34 (1.39) 4 - 12	7.53 (1.52) 4 - 12	7.00 (.92) 6 - 8	6.33 (1.15) 5 - 7	.10
Digit Span Backward Total Correct range	6.96 (2.28) 2 - 12	6.93 (2.36) 2 - 12	7.38 (2.15) 3 - 12	5.33 (2.08) 3 - 7	.32

Test	Total N = 217	Non-Carriers N=146	Single mutation (Heterozygotes) N=65	Two mutations (Compound heterozygotes/ Homozygotes) N=6	P value
Digit Span Backward* Length range	5.40 (1.72) 2 - 11	5.52 (1.90) 2 - 11	5.22 (1.21) 3 - 7	4.33 (.57) 4 - 5	.42

Values with different superscript letters reflect significant differences across groups on *post-hoc* testing; a=highest score, b=lowest score. For Trail Making Test, parts A and B and CVLT-II False Positives, low raw scores are indicative of better performance.

* Digit Span subtest was administered to a subset of subjects in each of the four groups specified above (n = 93; 62, 27, 4).