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## The relationship between Obsessive-Compulsive symptoms and *PARKIN* genotype: The CORE-PD study

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## Abstract

**Background**—Few studies have systematically investigated the association between *PARKIN* genotype and psychiatric co-morbidities of PD. *PARKIN*-associated PD is characterized by severe nigral dopaminergic neuronal loss, a finding that may have implications for behaviors rooted in dopaminergic circuits such as obsessive-compulsive symptoms (OCS).

**Methods**—The Schedule of Compulsions and Obsessions Patient Inventory (SCOPI) was administered to 104 patients with early-onset PD and 257 asymptomatic first-degree relatives. Carriers of one and two *PARKIN* mutations were compared to non-carriers.

**Results**—Among patients, carriers scored lower than non-carriers in adjusted models (one-mutation: 13.9 point difference,  $p=0.03$ ; two-mutation: 24.1,  $p=0.001$ ), where lower scores indicate less OCS. Among asymptomatic relatives, there was a trend towards the opposite: mutation carriers scored higher than non-carriers (one mutation  $p = 0.05$ ; two mutations  $p = 0.13$ ).

**Conclusions**—First, there was a significant association between *PARKIN* mutation status and obsessive-compulsive symptom level in both PD and asymptomatics, suggesting that OCS might represent an early non-motor dopamine-dependent feature. Second, irrespective of disease status, heterozygotes were significantly different than non-carriers suggesting that *PARKIN* heterozygosity may contribute to phenotype.

## Keywords

Parkinson's; neuropsychological; obsessive-compulsive; parkin

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## 1. INTRODUCTION

Few studies have systematically investigated the association between *PARKIN* genotype and psychiatric co-morbidities of PD.<sup>1-3</sup> We previously found no association between mutation status and depression among PD patients, but showed that asymptomatic carriers of two mutations had higher rates of depression than asymptomatic non-carriers, adding further support to evidence that depression is a prodromal symptom.<sup>4</sup> Obsessive-compulsive (OC) symptoms have been hypothetically linked to PD because both conditions involve the frontostriatal circuits.<sup>5,6</sup> In the present study, we sought to investigate the association between *PARKIN* genotype and the presence of OC symptoms (OCS), in persons with EOPD and their asymptomatic relatives, all of whom were participants in the Consortium on Risk for Early-Onset Parkinson Disease study (CORE-PD).<sup>7</sup> *PARKIN*-associated PD, in the case of homozygotes or compound heterozygotes, is, in contrast to sporadic PD, associated with more severe nigral dopaminergic neuronal loss but minimal involvement of other nuclei such as the raphe nucleus.<sup>8</sup> We hypothesized that the more severe nigropathy of *PARKIN*-associated PD would be associated with greater OCS. We also predicted that asymptomatic carriers of *PARKIN* mutations would endorse higher OCS given evidence that they also have dopaminergic dysfunction.<sup>9,10</sup>

## 2. METHODS

### 2.1. Participants

Patients with EOPD defined by age at onset  $\leq$  50 years and their asymptomatic first degree relatives were recruited from 17 sites participating in the CORE PD study).<sup>7,11</sup> Institutional review board approval was obtained at all sites. Patients with secondary parkinsonism, Parkinson plus, clinically-defined dementia with Lewy bodies or dementia predating motor symptoms were excluded.

The analyses were performed on 104 EOPD patients [23 with one *PARKIN* mutation and 26 with two mutations (19 compound heterozygotes and 7 homozygotes)] and on 257 of their first degree asymptomatic relatives [80 with 1 *PARKIN* mutation and 6 with two *PARKIN* mutations (5 compound heterozygotes and 1 homozygote)].

### 2.2. Molecular genetic analyses

Participants were genotyped for known pathogenic mutations in *SNCA*, *PARKIN*, *GBA*, *LRRK2*, *PINK-1*, *DJ-1* and the *PARKIN* gene was fully sequenced and assayed for dosage analysis as previously described.<sup>12-15</sup> Carriers of mutations in genes other than *PARKIN* were excluded.

### 2.3. Clinical and neuropsychological evaluation

The clinical evaluation of CORE-PD participants has been previously described.<sup>7,11</sup> Psychiatric evaluation included the Beck Depression Inventory-II and the SCOPI, a validated, self-report inventory composed of 5 subscales (checking, cleanliness, compulsive rituals, hoarding and pathological impulses) that has excellent internal consistency and test-retest reliability.<sup>16</sup> The total score sums the first three subscales (referred to herein as SCOPI-OCD) reflecting the core symptoms of OCD whereas the other two (hoarding and pathological impulses) evaluate different constructs.<sup>16</sup> Higher scores indicate more symptoms. BDI-II scores for 88/104 probands and 218/257 relatives were previously reported.<sup>4</sup>

### 2.4. Statistical analysis

Demographics, clinical and neuropsychological characteristics were compared between one- and two-mutation carriers and non-carriers in patients and asymptomatic relatives using *t*-tests and  $\chi^2$  tests as appropriate. Linear regression models were used to assess the association between mutation status (zero, one or two *PARKIN* mutations) and SCOPI-OCD score (continuous outcome) in models either unadjusted or adjusted for age, gender, and dopaminergic medication (measured in levodopa and ropinirole equivalents) and any covariates associated with SCOPI-OCD at *p* 0.10 in bivariate analyses: depression (based on BDI $\geq$ 15, an adjusted cutoff for diagnosis of depression)<sup>17</sup>, language (English or Spanish), and in the asymptomatic relatives, mild cognitive impairment based on consensus diagnosis.<sup>11</sup> Antidepressant use and UPDRS III were not significantly associated with outcome.

Logistic regression models were also used to test the association between membership in the highest tertile (i.e. higher OC symptom endorsement) and *PARKIN* genotype. To account for familial correlations in the relatives, we used backwards-stepwise regression with Generalized Estimating Equations (GEE). The association between genotype and the other two SCOPI subscales, hoarding and pathological impulses (eTables 3 and 4) was measured.

Finally, we tested the association between having EOPD and OCS using backwards-stepwise regression with GEE, first among non-carriers and then among *PARKIN* carriers (excluding 2-mutation carriers who may in fact be pre-symptomatic).

### 3. RESULTS

Demographic and clinical characteristics by mutation status are presented in Table 1.

#### 3.1. SCOPI in EOPD patients

In unadjusted models, *PARKIN* mutation carriers had lower SCOPI scores than non-carriers (two-mutation: 13.2 points lower,  $p = 0.02$ ; one-mutation: 10.2 points lower,  $p = 0.07$ ). In adjusted models, carrying one or two mutations was associated with a lower score: one-mutation carriers scored 13.9 points lower (95% CI:  $-26.1$  to  $-1.6$ ,  $p = 0.03$ ) than PD non-carriers; two-mutation carriers 24.1 points lower (95% CI:  $-38.5$  to  $-9.7$ ,  $p = 0.001$ ) than non-carriers (Table 2). Mutation carriers were less likely to score in the highest SCOPI-OCD tertile (one mutation: OR = 0.236,  $p = 0.03$ ; two mutations: OR = 0.109,  $p = 0.01$ ) (eTable 1).

The association was similar after adding depression (categorical) to the model (one-mutation:  $p=0.06$ ; two-mutation:  $p=0.004$ ; Table 2). Because the PD probands exhibited a wide range of BDI-II scores (0–33, mean 10.1, SD 8.2) we repeated the analyses after excluding subjects with scores  $\geq 28$  (i.e. severe depression)<sup>18</sup> and results were similar (eTable 2). The association between mutation status and OCS was similar in both English and Spanish-tested groups though did not reach statistical significance in the latter, [among the English-tested: one- and two-mutation carriers scored 11 points ( $p = 0.1$ ) and 18.7 points lower ( $p = 0.03$ ) respectively]. Finally, scores on the Hoarding and Pathological Impulses subscales of the SCOPI were also lower in mutation carriers but differences did not reach significance (eTables 3 and 4).

#### 3.2. SCOPI in asymptomatic first degree relatives

Among asymptomatic relatives the association was reversed. Carriers of one or two mutations had *higher* SCOPI-OCD scores than non-carriers in unadjusted models ( $p=0.05$  and  $p= 0.02$  respectively, Table 2). In models adjusted for family membership, age, gender, language, depression and MCI, this difference was significant for one-mutation carriers (8.2 points higher,  $p = 0.02$ ) but not for two-mutation carriers ( $n = 6$ ; 8.1 points higher,  $p = 0.14$ ; Table 2). In language-stratified analyses, the differences were of similar magnitude but reached significance only when comparing heterozygotes to non-carriers among those tested in English.

### 3.3. Effect of EOPD on SCOPI-OCD score

Among *PARKIN* heterozygotes, those with PD endorsed significantly less OCS than asymptomatic carriers when adjusting for age, gender, testing language and depression (7.7 point difference,  $p = 0.005$ ). When including only non-carriers there was no significant difference in SCOPI scores between probands and their asymptomatic relatives ( $p = 0.21$ ).

## 4. DISCUSSION

A characteristic phenotype for *PARKIN*-associated PD is emerging. In addition to the early age at onset, slower motor progression and excellent response to dopaminergic medications,<sup>1,2,7,19,20</sup> *PARKIN* PD homozygotes or compound heterozygotes also have a distinctive non-motor symptom profile, which includes normal olfaction,<sup>21</sup> and less cognitive impairment.<sup>11</sup> The present finding of an association between *PARKIN* mutation status and level of OCS further broadens this phenotype.

We demonstrated a dose-response association between mutation status and level of OCS endorsement, the direction of which differed based on PD status. Contrary to our predictions, PD patients with one or two mutations endorsed a *lower* level of symptoms than non-carriers whereas asymptomatic relatives with one or two mutations endorsed *more* OC symptoms.

Both dopamine and serotonin contribute to frontostriatal networks and may be relevant to OCS.<sup>22</sup> Indeed, polymorphisms linked to OCD have been identified in genes related to serotonin, epinephrine and dopamine function.<sup>23</sup> Thus it is possible that among PD patients, *PARKIN* carriers endorsed less OCS because compared to sporadic PD, they have less widespread neurodegeneration and are less likely to have involvement of the raphe nucleus, for instance, which is the main serotonin nucleus.<sup>8</sup> In contrast, the higher level of OCS among asymptomatic *PARKIN* carriers compared to non-carriers could relate to the mild dopaminergic dysfunction, corticostriatal reorganization and striatal structural changes that have been observed on PET and MRI imaging of asymptomatic *PARKIN* carriers, including heterozygotes.<sup>9,10,24,25</sup>

Considering only *PARKIN* carriers (and including only heterozygotes), we found that the PD patients had lower OCS than the asymptomatic relatives. If one assumes that the dopamine dysfunction is more severe in the PD than in the asymptomatics, and considering that this is a group likely to have a 'pure dopaminergic disease',<sup>11,26</sup> then the paradoxically lower level of OCS in those with PD, despite a more severe dopamine deficiency could be explained by analogy to Huntington's disease (HD). In HD, among pre-symptomatic at-risk individuals, it was shown that the level of OCS (also measured using SCOPI) was in fact lowest (and not different from controls) in the nearest-to-onset whereas the mid- and far-to-onset had the highest level of symptoms, even though they presumably have less dopaminergic dysfunction.<sup>27</sup>

A second finding of this study is that heterozygotes were significantly different than non-carriers, in both the proband and asymptomatic groups. The pathogenicity of single *PARKIN* mutations remains controversial. Though heterozygotes have some features of sporadic PD

such as loss of smell,<sup>21</sup> and Lewy bodies;<sup>28,29</sup> age at onset is younger in heterozygotes than non-carriers;<sup>7</sup> and asymptomatic heterozygotes have neuroimaging evidence of basal ganglia involvement.<sup>9,10,24,25</sup> Our finding that *PARKIN* heterozygotes regardless of PD status were significantly different than non-carriers suggests that *PARKIN* heterozygosity may contribute to phenotype.

Strengths of our study include the large number of genotyped and extensively phenotyped individuals, allowing for adjustment for confounding variables. Limitations include the cross-sectional design that does not allow us to draw anything more than speculative conclusions about the progression of dopamine loss and how this might relate to OC symptoms. Second, we are not implying any of the subject groups exhibited a level of symptoms suggestive of OCD since mean scores (whole group mean 39.6, SD 23.0) were lower than scores reported in OCD patients (mean 107.29, SD 19.4) and also lower than those of healthy adults (mean 79.4, SD 14.8);<sup>16</sup> though importantly, scores are not age-adjusted, an important consideration since OCS tend to decline throughout the lifespan.<sup>30</sup> Finally, we assume in our discussion that asymptomatic non-carriers have a normal dopaminergic system. However, because they are 1<sup>st</sup> degree relatives of EOPD patients, they may also carry an unidentified genetic risk factor for PD and dopaminergic dysfunction.

Future longitudinal studies focusing on differences in behaviors such as cognitive flexibility or harm avoidance rather than psychopathology are needed to better understand the contribution of *PARKIN* and the role of dopamine in determining these behaviors. Furthermore, only longitudinal studies can address whether asymptomatic *PARKIN* carriers will go on to develop PD and whether certain OC behaviors should be considered part of the non-motor prodromal stage.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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**Table 1**  
Demographic and clinical characteristics of probands and asymptomatic 1<sup>st</sup> degree relatives by *PARKIN* genotype

Characteristic	PD probands				Asymptomatic relatives				p-value#
	Non-carriers n=55	1 <i>PARKIN</i> mutation n=23	2 <i>PARKIN</i> mutations n=26	p-value#	Non-carriers n=171	1 <i>PARKIN</i> mutation n=80	2 <i>PARKIN</i> mutations n=6	p-value#	
Age	54.1 (8.2)	49.2 (9.9)	51.6 (11.5)	0.11	47.6 (17.2)	48.8 (18.8)	32.7 (11.1)	0.10	
Female sex (%)	42	35	42	0.83	59.6	58.2	66.7	0.91	
Test language Spanish (%)	9	14	21	0.40	9.8	13.5	20	0.54	
Education (years)	15.2 (3.0) <sup>a</sup>	15.7 (2.7) <sup>a</sup>	13.5 (3.4) <sup>b</sup>	0.02	14.4 (2.9)	14.5 (3.0)	13.8 (2.0)	0.88	
Disease duration (years)	11.8 (6.1) <sup>a</sup>	13.7 (7.2) <sup>a</sup>	21.4 (11.0) <sup>b</sup>	<0.01	--	--	--	--	
UPDRS III score	21.3 (8.4)	21.7 (7.3)	20.3 (7.4)	0.81	--	--	--	--	
Levodopa daily dose (mg)	494 (367)	491 (411)	471 (421)	0.97	--	--	--	--	
Dopamine agonist daily dose (mg) <sup>*</sup>	9.2 (13.5)	5.7 (8.5)	5.7 (9.8)	0.34	--	--	--	--	
Taking anti-depressant (%)	25.5	18.2	7.7	0.17	3.2	6.5	16.7	0.16	
BDI-II score	11.6 (8.9)	8.7 (8.1)	8.3 (6.7)	0.17	5.1 (5.9)	3.7 (4.7) <sup>a</sup>	9.8 (7.7) <sup>b</sup>	0.02	
Depressed (BDI <sub>II</sub> ≥ 15) (%)	31.5	21.7	29.2	0.69	8.4	5.0 <sup>a</sup>	33.3 <sup>b</sup>	0.04	
MMSE score	29.0 (1.3)	29.2 (1.0)	28.9 (1.6)	0.69	29.2 (2.2)	29 (2.3)	30 (0.0)	0.55	
Mild cognitive impairment (%)	41	59	58	0.21	31.4	32.2	33.3	0.99	
SCOP1 total (sum 5 items)	56.4 (28.0)	43.3 (26.3)	40.9 (29.8)	0.04	45.5 (27.6) <sup>a</sup>	54.4 (26.3) <sup>b</sup>	69.2 (28.4)	0.01	
SCOP1 OCD (sum 1 <sup>st</sup> 3 items)	45.1 (22.1) <sup>a</sup>	34.8 (21.6)	31.8 (24.3) <sup>b</sup>	0.03	36.9 (22.7) <sup>a</sup>	44.2 (21.6) <sup>b</sup>	59.3 (27.8) <sup>b</sup>	0.01	
Obsessive Checking	18.8 (11.9) <sup>a</sup>	11.7 (10.2) <sup>b</sup>	11.2 (10.8) <sup>b</sup>	0.01	13.4 (10.6) <sup>a</sup>	16.2 (11.4) <sup>a</sup>	23.7 (9.5) <sup>b</sup>	0.02	
Obsessive Cleanliness	16.9 (7.5)	14.6 (7.6)	15.4 (9.5)	0.45	15.6 (8.5)	18.2 (7.6)	21.3 (11.1)	0.03	
Compulsive Rituals	9.3 (7.6) <sup>a</sup>	8.6 (6.3)	5.2 (5.7) <sup>b</sup>	0.05	7.9 (7.1)	9.8 (6.7)	14.3 (9.2)	0.02	
Hoarding	7.3 (5.1)	5.0 (4.4)	5.9 (5.4)	0.15	6.3 (5.2)	7.1 (4.6)	6.0 (4.1)	0.44	
Pathological Impulses	4.0 (4.7)	3.5 (3.6)	3.2 (4.5)	0.72	2.3 (3.2)	3.1 (3.6)	3.8 (5.0)	0.15	

Note. UPDRS = United Parkinson's Disease Rating Scale. BDI = Beck Depression Inventory. MMSE = Mini-Mental State Examination. SCOP1-OCD = Schedule of Compulsions, Obsessions and Pathological Impulses – Obsessive-Compulsive subscales. Values are means and standard deviations (in parentheses) unless otherwise indicated.

# P-values represent the 3-way comparison using analysis of variance (ANOVA) except for sex, testing language, proportion taking anti-depressant, proportion depressed and proportion with mild cognitive impairment, which were calculated with Fisher's exact. Values with different superscript letters differ significantly on post-hoc testing for p<0.05.

\* Dopamine agonist dose calculated in ropinirole equivalents<sup>27</sup>

**Table 2**

Association between SCOPI-OCD score and *PARKIN* status among PD probands and asymptomatic first degree relatives in linear models

SCOPI-OCD score	PD probands			Asymptomatic relatives		
	Non-carriers	Mean difference in SCOPI OCD score compared to non-carriers (95% CI) p-value		Non-carriers	Mean difference in SCOPI OCD score compared to non-carriers (95% CI) p-value	
		<i>PARKIN</i> 1 mutation	<i>PARKIN</i> 2 mutations		<i>PARKIN</i> 1 mutation	<i>PARKIN</i> 2 mutations
Unadjusted model	45.1	-10.2 -21.3 to +0.9 p=0.07	-13.2 -23.9 to -2.6 p=0.02	36.9	+7.3 +0.005 to +14.6 p=0.05	+22.5 +3.7 to +41.72 p=0.02
Model 1: adjusted for age, gender, language, disease duration, levodopa equivalent and ropinirole equivalent doses (in PD), and MCI (in asymptomatic)	48.7	-13.9 -26.1 to -1.6 p=0.03	-24.1 -38.5 to -9.7 p=0.001	36.9	+7.2 -0.005 to +14.3 0.05	+15.4 -4.4 to +35.3 0.13
Model 2: Model 1 + depression (based on BDI 15)	47.9	-11.9 -24.1 to +0.3 p=0.06	-21.6 -36.1 to -7.1 p=0.004	36.6	+8.2 +1.5 to +15.0 p=0.02	+8.1 -2.5 to +18.7 p=0.14

Note. SCOPI-OCD = Schedule of Compulsions, Obsessions and Pathological Impulses – Obsessive-Compulsive subscales. BDI = Beck Depression Inventory.