

parkin-associated Parkinson disease



Francesca Morgante, MD, PhD
 Alfonso Fasano, MD, PhD
 Monia Ginevrino, PhD
 Simona Petrucci, MD
 Lucia Ricciardi, MD, PhD
 Francesco Bove, MD
 Chiara Criscuolo, MD, PhD
 Marcello Moccia, MD
 Anna De Rosa, MD, PhD
 Chiara Sorbera, MD
 Anna Rita Bentivoglio, MD, PhD
 Paolo Barone, MD, PhD
 Giuseppe De Michele, MD, PhD
 Maria Teresa Pellecchia, MD, PhD
 Enza Maria Valente, MD, PhD

ABSTRACT

Objective: The aim of this multicenter, case-control study was to investigate the prevalence and severity of impulsive-compulsive behaviors (ICBs) in a cohort of patients with *parkin*-associated Parkinson disease (PD) compared to a group of patients without the mutation.

Methods: We compared 22 patients with biallelic *parkin* mutations (*parkin*-PD) and 26 patients negative for *parkin*, *PINK1*, *DJ-1*, and *GBA* mutations (PD-NM), matched for age at onset, disease duration, levodopa, and dopamine agonist equivalent daily dose. A semistructured interview was used to diagnose each of the following ICBs: compulsive sexual behavior, compulsive buying, binge eating, punting, hobbyism, and compulsive medication use. The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) was adopted to rate ICB severity.

Results: Frequency of patients with at least one ICB was comparable between *parkin*-PD and PD-NM. Nevertheless, when analyzing the distribution of specific ICBs, a higher frequency of compulsive shopping, binge eating, and punting/hobbyism was found in the *parkin*-PD group. Compared to PD-NM, *parkin*-PD patients with ICB had younger onset age and higher frequency of smokers; in 5 patients, ICB had predated PD onset. Total and partial (compulsive buying, compulsive sexual behavior, binge eating, hobbyism/punting) QUIP-RS scores were higher in patients with *parkin*-PD compared to patients with PD-NM. Logistic regression analysis showed that the presence of *parkin* mutations was associated with smoking status and higher QUIP-RS total score.

Conclusions: Our data expand the *parkin*-associated phenotypic spectrum demonstrating higher frequency and severity of specific ICBs, and suggesting an association between the *parkin* genotype, smoking status, and ICB severity. *Neurology*® 2016;87:1436-1441

Correspondence to
 Dr. Morgante:
fmorgante@gmail.com

GLOSSARY

D-Ag = dopamine agonist; **DSM-IV** = *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition); **EOPD** = early-onset Parkinson disease; **ICB** = impulsive-compulsive behavior; **LEDD** = levodopa equivalent daily dose; **OCS** = obsessive-compulsive symptoms; **parkin-PD** = Parkinson disease with *parkin* mutation; **PD** = Parkinson disease; **PD-NM** = Parkinson disease-negative for mutations; **QUIP-RS** = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

The term *early-onset Parkinson disease* (EOPD) refers to Parkinson disease (PD) with age at onset between the third and the fifth decade, slow progression, good response to levodopa treatment, and low burden of cognitive symptoms.^{1,2} However, patients with EOPD are more likely to develop psychiatric and behavioral disturbances, specifically depression, anxiety, and impulsive-compulsive behaviors (ICBs).³ These include impulse control disorders such as pathologic gambling, compulsive sexual behavior, compulsive buying and binge eating, and compulsive behaviors such as punting and compulsive use of dopamine replacement therapy (also known as dopamine dysregulation syndrome).⁴

From the Department of Clinical and Experimental Medicine (F.M., C.S.), University of Messina, Italy; Morton and Gloria Shulman Movement Disorders Clinic and the Edmond J. Safra Program in Parkinson's Disease (A.F.), Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Canada; Department of Neurology and Psychiatry (S.P.), Sapienza University of Rome, Italy; Sobell Department of Motor Neuroscience and Movement Disorders (L.R.), Institute of Neurology, University College London, UK; Department of Geriatrics, Neuroscience and Orthopedics (F.B., A.R.B.), Università Cattolica del Sacro Cuore, Rome; Department of Neurosciences, Reproductive and Odontostomatological Sciences (C.C., M.M., A.D.R., G.D.M.), Federico II University, Naples; Department of Medicine and Surgery (M.G., M.M., P.B., M.T.P., E.M.V.), Neuroscience Section, University of Salerno, and Neurogenetics Unit (E.M.V.), IRCCS Santa Lucia Foundation, Rome, Italy.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Editorial, page 1426

Supplemental data
 at Neurology.org

Table 1 Demographic and clinical features of patients with parkin-PD and PD-NM

	Parkin-PD (n = 22)	PD-NM (n = 26)	p Value
Sex, F/M	9/13	9/17	0.7
Age, y	52.6 ± 10.9	55.1 ± 8.5	0.2
Age at onset, y	31.2 ± 10.6	36.9 ± 8.1	0.06
Disease duration, y (range)	21.9 ± 10.9 (3-43)	18.2 ± 9.8 (5-46)	0.2
UPDRS-III score	18.9 ± 9.6	21.0 ± 8.5	0.5
LEDD, mg	707.9 ± 523.3	868.3 ± 505.0	0.1
D-Ag LEDD, mg	159.7 ± 131.4	231.4 ± 210.3	0.6
Phenotype of PD, T/AR	13/9	13/13	0.5
Most affected side, R/L/U	6/14/2	10/16/0	0.2
RBD, yes/no	6/15	3/23	0.2
Depression, yes/no	8/14	15/11	0.1
Psychosis, yes/no	1/21	5/21	0.2
Dementia, yes/no	3/19	1/25	0.3
Smoking, yes/no	9/13	1/25	0.003 ^a
ICB, yes/no	15/7	13/13	0.2
QUIP-RS score	21.9 ± 19.1	6.7 ± 8.5	0.02 ^a

Abbreviations: AR = akineto-rigid; D-Ag = dopamine agonists; ICB = impulsive-compulsive behavior; LEDD = levodopa equivalent daily dose; parkin-PD = Parkinson disease with *parkin* mutation; PD-NM = Parkinson disease-negative for mutations; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; RBD = rapid eye movement sleep behavior disorder; T = tremor dominant; U = unclear; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.

Values reported are means ± SD. Categorical variables compared by Fisher exact test.

^aIndicates differences ($p < 0.05$).

EOPD might be inherited in autosomal recessive fashion, and it is most frequently caused by biallelic mutations in the *parkin* gene.⁵ Previous studies aiming to define the neuropsychiatric profile of *parkin*-associated PD (parkin-PD) have failed to demonstrate a higher frequency of either depression⁶ or obsessive-compulsive symptoms (OCS)⁷ in symptomatic carriers of *parkin* mutations as compared to noncarriers. Nevertheless, no study has systematically explored the occurrence and spectrum of ICB in parkin-PD. Therefore, it remains unclear whether ICB might be related to specific genetic mutations or simply to an early age at onset, as previously reported.⁴

The aim of this multicenter, case-control study was to investigate the prevalence and severity of ICB in a cohort of patients with parkin-PD compared to a group of patients with nonmutated PD (PD-NM) matched for demographic and clinical features.

METHODS **Selection of patients.** From the genetic database at the CSS Mendel Institute in Rome, including an overall

number of 2,124 patients with PD, of whom 791 had EOPD (age at onset <50 years), we identified 36 patients who were carriers of pathogenic biallelic mutations of the *parkin* gene (parkin-PD). Twenty-two patients with parkin-PD agreed to take part in this study (table e-1 at Neurology.org). Referral centers were 4 tertiary movement disorders outpatient clinics based in Rome, Naples, Salerno, and Messina. From the same database, we selected a cohort of 26 controls with EOPD (PD-NM) in whom we excluded point mutations and exon rearrangements in the *parkin* gene. Moreover, in all cases and controls, we excluded the occurrence of point mutations, small insertions/deletions, and splice-site mutations in the *PINK1*, *DJ-1*, and *GBA* genes by direct Sanger sequencing; we also excluded the presence of single or multiexon deletions or multiplications of *PINK1*, *DJ-1*, and *SNCA* by multiplex ligation-dependent probe amplification analysis. Furthermore, we used TaqMan genotyping to exclude the Contursi mutation p.A53T in the *SNCA* gene and the common mutations p.G2019S and p.R1441C in the *LRKK2* gene.

Parkin-PD and PD-NM patients were matched for the following demographic and clinical features: sex, age at study entry, age at disease onset, disease duration, PD phenotype, most affected side, and levodopa equivalent daily dose (LEDD).⁸ LEDD was also considered in terms of dopamine agonist (D-Ag) LEDD. Smoking habits were also retrieved (smoker/nonsmoker at study entry). In all patients, the motor section of the Unified Parkinson's Disease Rating Scale, Part III, was assessed in the "on" state to evaluate disease severity. The presence/absence of the following psychiatric and cognitive features was recorded: psychosis (illusions, hallucinations, delusions) according to National Institute of Neurological Disorders and Stroke/National Institute of Mental Health criteria,⁹ and depression and dementia according to DSM-IV criteria. The presence of rapid eye movement sleep behavior disorder was diagnosed based on a single question as in Postuma et al.¹⁰: "Have you ever been told, or suspected yourself, that you seem to 'act out your dreams' while asleep (for example, punching, flailing your arms in the air, making running movements, etc.)?"

ICB assessment. A semistructured interview using accepted diagnostic criteria¹¹ for pathologic gambling, compulsive buying, compulsive sexual behavior, binge eating, punting, and compulsive use of dopamine replacement therapy (anytime in the past 6 months) was used to reach the diagnosis of each of these ICBs. In addition, the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS), a rating scale designed to measure severity of ICB in PD, was administered to all patients.^{12,13} The QUIP-RS is a patient-filled questionnaire composed by 4 questions for each ICB, which have to be answered on a 5-point Likert scale. Total impulse control disorder score ranges from 0 to 64; total QUIP-RS score ranges from 0 to 112. In all patients diagnosed with ICB, we also evaluated duration of ICB, their occurrence before disease onset, and presence of a positive family history of ICB or alcohol and drug abuse.

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethic committee of the recruiting centers and conformed to the Declaration of Helsinki. All patients gave their written informed consent before participation.

Statistical analysis. Comparisons between groups were made using the Fisher exact test or the χ^2 test for categorical variables. Nonparametric Mann-Whitney *U* test was used to compare continuous variables. Correlations between QUIP-RS and age

at onset, disease duration, LEDD, D-Ag LEDD, and ICB duration were explored by Spearman rank correlation. Logistic regression was used to verify the association between ICB (presence/absence) and the following variables: age at onset, LEDD, D-Ag LEDD, and smoking status. Moreover, logistic regression was also used to test possible associations between mutation carrier status (presence/absence of biallelic mutations in the *parkin* gene) and the following variables: QUIP-RS, ICB duration, smoking status, and ICB before PD onset. Significance level was set at $p < 0.05$. Unless otherwise stated, data are given as mean \pm SD.

RESULTS Parkin-PD (n = 22) and PD-NM (n = 26) were comparable for all the demographic and clinical variables taken into account but smoking habit, which was more frequent in the parkin-PD group ($p = 0.003$; table 1).

The frequency of patients with at least one ICB was comparable between parkin-PD and PD-NM (table 1). Nevertheless, when analyzing distribution of specific ICBs in each group, Fisher exact test disclosed differences between the 2 groups, with higher frequency of compulsive shopping, binge eating, and punning/hobbyism in the parkin-PD group (figure 1). Moreover, QUIP-RS scores were higher in the parkin-PD compared to the PD-NM group (table 1).

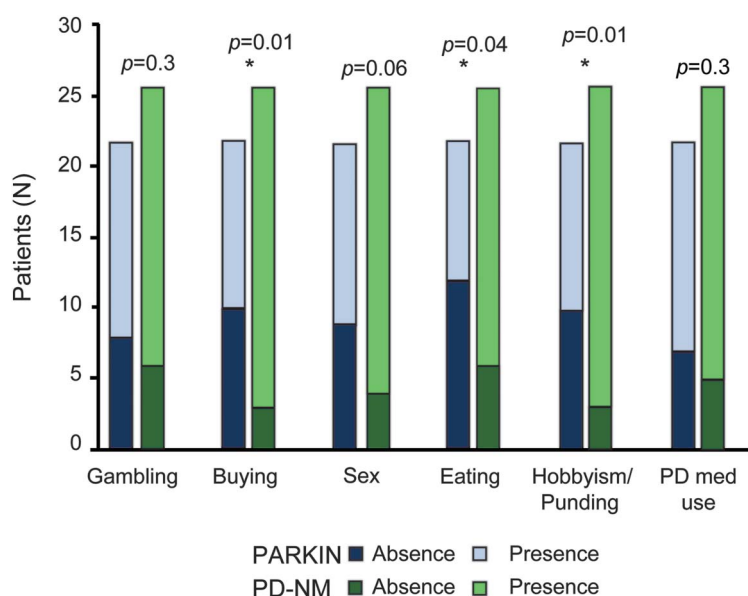
When comparing only patients with ICB, the 2 groups of patients remained similar for most demographic and clinical features, except for a younger age at PD onset, a higher frequency of smokers than in the PD-NM group, and a lower LEDD in parkin-PD (table 2). Again, the severity of ICB, as measured by total QUIP-RS, was greater in the parkin-PD

group compared to PD-NM (table 2), with higher values in the subscores related to compulsive buying, compulsive sexual behavior, binge eating, and hobbyism/punding (figure 2). Accordingly, 2-way analysis of covariance adjusted for age at onset confirmed that patients with parkin-PD scored higher at QUIP-RS ($F = 9.5$, $p = 0.005$).

In addition, we compared in the parkin-PD group patients with (n = 15) and without (n = 7) ICB; we were unable to disclose any difference for age ($p = 0.1$), age at onset ($p = 0.07$), disease duration ($p = 0.7$), total LEDD ($p = 0.2$), or D-Ag LEDD ($p = 0.1$). Similar findings were demonstrated in the PD-NM group categorizing patients by presence (n = 13) or absence (n = 13) of ICB (age: $p = 0.6$, age at onset: $p = 0.6$, disease duration: $p = 0.2$, total LEDD: $p = 0.6$, or D-Ag LEDD: $p = 0.9$).

Univariate correlational analysis in patients with ICB disclosed a positive relation between QUIP-RS and ICB duration ($p = 0.03$, $r = 0.4$) but not with age at onset ($p = 0.09$, $r = -0.3$). No correlations were found between QUIP-RS and disease duration, total LEDD, or D-Ag LEDD. Logistic regression analysis (table 3) did not demonstrate any association of ICB with presence of *parkin* mutations, age at onset, or D-Ag LEDD, whereas association with age at onset and disease duration showed a statistical trend. Nevertheless, the *parkin* genotype was associated with smoking status and higher QUIP-RS total score (table 3). Finally, multiple linear regression analysis did not show an association of QUIP-RS with total LEDD ($p = 0.27$), D-Ag LEDD ($p = 0.50$), age at onset ($p = 0.15$), or disease duration ($p = 0.48$).

Figure 1 ICBs in parkin-PD and nonmutated PD



Frequency of specific impulsive-compulsive behaviors (ICBs) in *parkin* homozygous and in nonmutated Parkinson disease (PD-NM). Parkin-PD disclosed a higher frequency of compulsive shopping, binge eating, punning/hobbyism, and abuse of PD medications.

DISCUSSION Several conditions have been established as risk factors for ICB in PD, including younger age, male sex, exposure to D-Ag and levodopa, smoking habit, marital status, and family history of gambling problems.^{4,14} However, it is still unknown whether genetic mutations represent predisposing factors for ICB. Recently, ICB was reported in 3 patients carrying mutations in *PINK1*, another gene responsible for autosomal recessive EOPD. They all presented hypersexuality, compulsive shopping, and binge eating; in addition, punning was also present in one patient.¹ A similar behavioral profile was reported in 2 brothers with *PINK1* mutation respectively presenting with pathologic gambling many years before PD onset and hypersexuality, punning, and hypomania¹⁵ and in one patient with *PINK1* mutation presenting with compulsive use of dopaminergic medications.¹⁶ Besides these case reports, no study has systematically evaluated the frequency and severity of these behavioral complications in autosomal recessive EOPD.

Table 2 Demographic and clinical features of patients with PD and ICB according to mutation status

	Parkin-PD (n = 15)	PD-NM (n = 13)	p Value
Sex, M/F	8/7	9/4	0.2
Age, y	50.5 ± 9.6	54.0 ± 7.4	0.2
Age at onset, y	28.9 ± 9.2	37.3 ± 9.9	0.02 ^a
Disease duration, y	22.5 ± 10.3	16.8 ± 9.7	0.09
UPDRS-III score	19.7 ± 7.4	18.2 ± 6.2	0.5
LEDD, total, mg	732.0 ± 514.4	969.0 ± 560.2	0.01 ^a
LEDD D-Ag, mg	208.9 ± 124.7	196.7 ± 152.6	0.8
RBD, yes/no	4/11	1/12	0.3
Depression, yes/no	7/8	8/5	0.5
Psychosis, yes/no	1/14	3/10	0.3
Dementia, yes/no	2/13	0/13	0.5
Smoking, yes/no	7/8	1/12	0.04 ^a
Family history of ICB, yes/no	3/11	0/13	0.2
ICB duration, y	9.5 ± 6.5	5.9 ± 4.5	0.08
ICB before PD onset, yes/no	5/10	0/13	0.04 ^a
QUIP-RS score	31.5 ± 15.2	13.5 ± 7.2	0.001 ^a

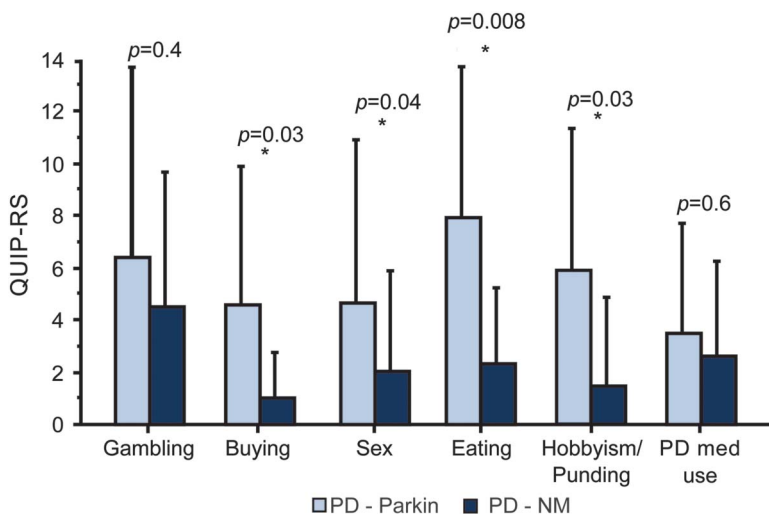
Abbreviations: D-Ag = dopamine agonists; ICB = impulsive-compulsive behavior; LEDD = levodopa equivalent daily dose; parkin-PD = Parkinson disease with *parkin* mutation; PD = Parkinson disease; PD-NM = Parkinson disease-negative for mutations; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale; RBD = rapid eye movement sleep behavior disorder; UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III.

Values reported are means ± SD. Categorical variables compared by Fisher exact test.

^aIndicates differences ($p < 0.05$).

In this case-control study, we sought to determine whether *parkin*-related EOPD might be associated with a higher frequency of ICB by assessing 2 cohorts

Figure 2 Severity of ICB in parkin-PD and nonmutated PD



Patients with parkin-PD disclose higher Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) scores for the following impulsive-compulsive behaviors (ICBs) compared to nonmutated Parkinson disease (PD-NM): compulsive shopping, hypersexuality, punning/hobbyism, abuse of PD medication.

of patients, one with *parkin*-mutated PD and one with nonmutated PD comparable for several variables involved in ICB development (age, age at onset, disease duration, LEDD, D-Ag LEDD). Although the occurrence of ICB did not correlate with the *parkin* genotype, *parkin* mutations influenced both the onset and severity of specific behavioral disturbances in the impulsive-compulsive spectrum. In particular, ICB was overall more severe in *parkin* carriers who also disclosed a higher frequency and severity of compulsive shopping, binge eating, and punning. Regarding hypersexuality, patients with parkin-PD reported a similar frequency but a more severe clinical expression. Moreover, ICB tended to occur earlier in patients with the *parkin* mutation, sometimes predating PD onset.

Univariate correlational analysis revealed a correlation of QUIP-RS with ICB duration. In line with this finding, it is possible to speculate that the observed increased severity in patients with the *parkin* mutation may be at least in part influenced by the age at PD onset, which tended to be younger in the parkin-PD group. However, the effect of genotype on QUIP-RS remained when adjusting for age at onset; in addition, age at onset was not correlated with QUIP-RS, neither in the univariate analysis nor in multiple linear regression analysis. These differences are also unlikely to depend on disparities in dopaminergic medication dosage, since patients with and without *parkin* mutation were matched both for total LEDD and D-Ag LEDD; nevertheless, the patients with parkin-PD and ICB had a lower total LEDD, supporting the hypothesis that they might be more sensitive to developing ICB with a lower dose of dopaminergic medications.

A novel datum from our study is the association between the *parkin* genotype and smoking status. This might have also accounted for the association between smoking and ICB, considering that smoking habit was more frequent in patients with parkin-PD and ICB compared to the nonmutated ICB group. Only one study had reported an inverse association between *parkin* mutation and smoking, demonstrating a higher frequency of *parkin* mutations among never-smoker Sikh Indians, in whom smoking is forbidden by religious texts.¹⁷ The relationship between smoking and PD has been explored in several studies in sporadic PD, which demonstrated an inverse association between PD and smoking,¹⁸ likely to be caused by low-sensation-seeking personality traits caused by dopaminergic denervation.¹⁹ Conversely, smoking has been positively associated with ICB in PD,^{4,20} in a dose-dependent manner and also independently by D-Ag use.²¹ Recent studies showed that smoking habits can result in motor and nonmotor correlates in PD, and, thus, nicotine and other

Table 3 Factors associated with ICB and with mutations in the *parkin* gene

	OR	95% CI	p Value
Factors associated with ICB			
Genotype (<i>parkin</i> -PD/PD-NM)	1.046	0.119-1.950	0.3064
Age at onset	2.996	0.844-1.011	0.0835
Disease duration	2.920	0.860-1.010	0.0875
LEDD, mg	1.997	1.000-1.003	0.1576
D-Ag LEDD, mg	0.019	0.119-1.950	0.8904
Factors associated with ICB and with mutations in the <i>parkin</i> gene			
QUIP-RS	5.263	0.822-0.985	0.0218 ^a
Smoking status (yes/no)	6.222	0.004-0.515	0.0126 ^a
ICB duration	1.254	0.874-1.639	0.2629
ICB before PD onset (yes/no)	1.363E-4	0.000	0.9907

Abbreviations: CI = confidence interval; D-Ag = dopamine agonists; ICB = impulsive-compulsive behavior; LEDD = levodopa equivalent daily dose; OR = odds ratio; *parkin*-PD = Parkinson disease with *parkin* mutation; PD = Parkinson disease; PD-NM = Parkinson disease-negative for mutations; QUIP-RS = Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale.

^aIndicates differences ($p < 0.05$).

cigarette components have been suggested to have a broad action on the heterogeneity of the clinical phenotype.²² Thus, it is tempting to speculate that smoking habit could somehow influence the severity of ICB in patients with *parkin* mutation. Supporting this hypothesis, IV administration of nicotine in the rat is associated with increased glucose utilization and increased dopaminergic transmission in the shell of the nucleus accumbens,²³ a limbic area involved in reward and addiction. Alternatively, patients with *parkin*-PD might be more prone to smoking as a manifestation of their ICB, as smoking and pathologic gambling also frequently co-occur in nonparkinsonian patients.²⁴

OCS were also reported to be more severe in patients with PD and ICB.⁷ Of note, a recent study showed lower levels of OCS in *parkin*-mutated compared to nonmutated PD, but highlighted a trend for higher OCS levels in asymptomatic *parkin* mutation carriers compared to noncarriers, suggesting that OCS may represent an early nonmotor dopamine-dependent feature.⁷ In this light, although we were not able to assess OCS in our patients, our observation of ICB predating PD onset in some *parkin* mutation carriers could also point at ICB as a potential early sign of dopaminergic dysfunction. Further studies are needed to thoroughly explore the association between OCS and ICB in patients with *parkin*-PD.

Besides these potential correlations, the mechanism underlying the increased ICB severity in *parkin*-associated PD still remains to be elucidated. An intriguing explanation may relate to the selective neurodegeneration of frontostriatal-limbic structures

observed in *parkin* carriers, as patients with PD and ICB were found to exhibit alterations of cortical thickness in the frontostriatal-limbic circuitry.¹³ Indeed, a functional neuroimaging study using an automated segmentation MRI method demonstrated decrease of gray matter volume in the caudate nuclei of *parkin*-PD compared to PD-NM²⁴; a similar finding was reported also by functional imaging studies by PET and SPECT, which demonstrated a severe dopaminergic denervation both in the caudate nuclei and the putamen in symptomatic *parkin*-PD.^{25,26} The caudate nucleus is part of the ventral striatum and is connected with the orbitofrontal cortex, an area involved in reward and stimulus-reinforcement association learning²⁷; specifically, the caudate nucleus receives converging projections from orbitofrontal cortex, dorsolateral prefrontal cortex, and parietal regions, supporting the role of this structure in the integration of reward, attention, and executive processes that occurs during spatial reinforcement learning.²⁸ In this light, it can be foreseen that functional neuroimaging studies would greatly help in the understanding of the neural basis of ICB symptoms in patients with *parkin*-PD.

We acknowledge that the number of study participants is small, because of the rarity of these genetic conditions. Indeed, our study sample is comparable to previous cohort studies exploring cognition and depressive symptoms in *parkin*-PD.^{6,7,29} Further studies in distinct cohorts of patients with and without the *parkin* mutation will be required to replicate our findings.

Our data expand the spectrum of *parkin*-associated PD phenotype demonstrating a higher frequency and severity of specific ICB related to compulsive behaviors; furthermore, our findings suggest an association between the *parkin* genotype and smoking status, which needs to be further explored in relation to the development of impulsive-compulsive behaviors.

AUTHOR CONTRIBUTIONS

Francesca Morgante and Enza Maria Valente: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Alfonso Fasano: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Monia Ginevrino, Simona Petrucci, Lucia Ricciardi, Francesco Bove, Chiara Criscuolo, Marcello Moccia, Anna De Rosa, Chiara Sorbera: acquisition of data, critical revision of the manuscript for important intellectual content. Anna Rita Bentivoglio, Paolo Barone, Giuseppe De Michele, Maria Teresa Pellicchia: analysis and interpretation, critical revision of the manuscript for important intellectual content.

STUDY FUNDING

This work was partly supported by the EU grant FP7 MEFOPA.

DISCLOSURE

F. Morgante has received honoraria as a consultant and on advisory boards from Medtronic and Chiesi. She has received honoraria for speaking from UCB Pharma, Medtronic, Lundbeck, Chiesi, AbbVie. She

serves on the editorial board of *Movement Disorders Clinical Practice* and *Frontiers in Movement Disorders*. A. Fasano has received grant support from the University of Toronto, the McLaughlin Centre, and the Michael J. Fox Foundation; he received speaking honoraria from UCB Pharma, Medtronic, Boston Scientific, AbbVie, Novartis, Chiesi Pharmaceutical, and TEVA; he is on an advisory board for AbbVie and provided consultancies for UCB Pharma, Medtronic, Boston Scientific, and AbbVie. M. Ginevrino, S. Petrucci, L. Ricciardi, F. Bove, C. Criscuolo, M. Moccia, A. De Rosa, C. Sorbera, and A. Bentivoglio report no disclosures relevant to the manuscript. P. Barone has received honoraria as a consultant and on advisory boards from Lundbeck, UCB, Zambon, PIAM. He has received honoraria for speaking from UCB, Zambon, Lundbeck, Chiesi, AbbVie. G. De Michele and M. Pellecchia report no disclosures relevant to the manuscript. E. Maria Valente has received grant support from the Italian Ministry of University and Research, the Italian Ministry of Health, Telethon Foundation Italy, the Pierfranco and Luisa Mariani Foundation ONLUS, and the European Research Council. She received honoraria for speaking from Medtronic. She serves on the editorial board of *BMC Neurology*, *Pediatric Research* and *Current Molecular Medicine*. Go to Neurology.org for full disclosures.

Received February 9, 2016. Accepted in final form May 2, 2016.

REFERENCES

- Ricciardi L, Petrucci S, Guidubaldi A, et al. Phenotypic variability of PINK1 expression: 12 years' clinical follow-up of two Italian families. *Mov Disord* 2014; 29:1561–1566.
- Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Frequency of known mutations in early-onset Parkinson disease: implication for genetic counseling; the Consortium on Risk for Early Onset Parkinson Disease Study. *Arch Neurol* 2010;67:1116–1122.
- Weintraub D, Burn DJ. Parkinson's disease: the quintessential neuropsychiatric disorder. *Mov Disord* 2011;26: 1022–1031.
- Weintraub D, Koester J, Potenza MN, et al. Impulse control disorders in Parkinson disease: a cross-sectional study of 3090 patients. *Arch Neurol* 2010;67:589–595.
- Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998;392:605–608.
- Srivastava A, Tang MX, Mejia-Santana H, et al. The relation between depression and parkin genotype: the CORE-PD study. *Parkinsonism Relat Disord* 2011;17:740–744.
- Sharp ME, Caccappolo E, Mejia-Santana H, et al. The relationship between obsessive-compulsive symptoms and PARKIN genotype: the CORE-PD study. *Mov Disord* 2015;30:278–283.
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov Disord* 2010;25:2649–2653.
- Ravina B, Marder K, Fernandez HH, et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007;22: 1061–1068.
- Postuma RB, Arnulf I, Hogl B, et al. A single-question screen for rapid eye movement sleep behavior disorder: a multicenter validation study. *Mov Disord* 2012;27: 913–916.
- Weintraub D, Hoops S, Shea JA, et al. Validation of the questionnaire for impulsive-compulsive disorders in Parkinson's disease. *Mov Disord* 2009;24:1461–1467.
- Weintraub D, Mamikonyan E, Papay K, Shea JA, Xie SX, Siderowf A. Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease—Rating Scale. *Mov Disord* 2012;27:242–247.
- Biundo R, Weis L, Facchini S, et al. Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. *Mov Disord* 2015;30:688–695.
- Weintraub D. Impulse control disorders in Parkinson's disease: prevalence and possible risk factors. *Parkinsonism Relat Disord* 2009;15(suppl 3):S110–S113.
- Ephraty L, Porat O, Israeli D, et al. Neuropsychiatric and cognitive features in autosomal-recessive early parkinsonism due to PINK1 mutations. *Mov Disord* 2007;22:566–569.
- Criscuolo C, Volpe G, De Rosa A, et al. PINK1 homozygous W437X mutation in a patient with apparent dominant transmission of parkinsonism. *Mov Disord* 2006;21: 1265–1267.
- Prabhakar S, Vinish M, Das CP, Anand A. Occurrence of PARK2 mutations in a never-smoker population with Parkinson's disease in North India. *Neuroepidemiology* 2010; 35:152–159.
- Nicoletti A, Pugliese P, Nicoletti G, et al. Voluntary habits and clinical subtypes of Parkinson's disease: the FRAGAMP case-control study. *Mov Disord* 2010;25: 2387–2394.
- Evans AH, Lawrence AD, Potts J, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2006;77:317–321.
- Bastiaens J, Dorfman BJ, Christos PJ, Nirenberg MJ. Prospective cohort study of impulse control disorders in Parkinson's disease. *Mov Disord* 2013;28:327–333.
- Valenca GT, Glass PG, Negreiros NN, et al. Past smoking and current dopamine agonist use show an independent and dose-dependent association with impulse control disorders in Parkinson's disease. *Parkinsonism Relat Disord* 2013;19:698–700.
- Moccia M, Mollenhauer B, Erro R, Picillo M, Palladino R, Barone P. Non-motor correlates of smoking habits in de novo Parkinson's disease. *J Parkinsons Dis* 2015;5:913–924.
- Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. *Nature* 1996;382:255–257.
- Bilgic B, Bayram A, Arslan AB, et al. Differentiating symptomatic Parkin mutations carriers from patients with idiopathic Parkinson's disease: contribution of automated segmentation neuroimaging method. *Parkinsonism Relat Disord* 2012;18:562–566.
- Pavese N, Khan NL, Scherfler C, et al. Nigrostriatal dysfunction in homozygous and heterozygous parkin gene carriers: an 18F-dopa PET progression study. *Mov Disord* 2009;24:2260–2266.
- Varrone A, Pellecchia MT, Amboni M, et al. Imaging of dopaminergic dysfunction with [123I]FP-CIT SPECT in early-onset parkin disease. *Neurology* 2004;63:2097–2103.
- Rolls ET. The orbitofrontal cortex and reward. *Cereb Cortex* 2000;10:284–294.
- Jarbo K, Verstynen TD. Converging structural and functional connectivity of orbitofrontal, dorsolateral prefrontal, and posterior parietal cortex in the human striatum. *J Neurosci* 2015;35:3865–3878.
- Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive and motor function in long-duration PARKIN-associated Parkinson disease. *JAMA Neurol* 2014;71:62–67.