Published in final edited form as:
Mov Disord. 2015 February ; 30(2): 278–283. doi:10.1002/mds.26065.

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

ME Sharp, MD[1], **E Caccappolo, PhD**[1], **H Mejia-Santana, MSc**[1], **M–X Tang, PhD**[1,2], **L Rosado, MD**[1], **M Orbe Reilly, MD**[1], **D Ruiz, BSc**[1], **ED Louis, MD, MSc**[1,2,3,4], **C Comella, MD**[5], **M Nance, MD**[6], **S Bressman, MD**[7,8], **WK Scott, PhD**[9], **C Tanner, MD, PhD**[10], **C Waters, MD**[1], **S Fahn, MD**[1], **L Cote, MD**[1,3], **B Ford, MD**[1], **M Rezak, MD, PhD**[12], **K Novak, PhD**[13,14], **JH Friedman, MD**[15,16], **R Pfeiffer, MD**[17], **H Payami, PhD**[18], **E Molho, MD**[19], **SA Factor**[20], **J Nutt, MD**[21], **C Serrano, MD**[22], **M Arroyo, MD**[22], **MW Pauciulo, BSc, MBA**[23], **WC Nichols, PhD**[23], **LN Clark, PhD**[2,24,25], **RN Alcalay, MD, MSc**[1,2], and **KS Marder, MD, MPH**[1,2,3,26]

[1]Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[2]Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Corresponding author: Karen S Marder, Taub Institute for Research on Alzheimer's and the Aging Brain, College of Physicians and Surgeons, Columbia University, 630 West 168th Street, Unit 16, New York, NY 10032 USA, ksm1@cumc.columbia.edu.

Financial Disclosures: The authors report no conflicts of interest.

Dr. Sharp, Dr. Caccappolo, Ms. Mejia-Santana, Dr. Tang, Dr. Rosado, Ms. Ruiz, Dr. Orbe Reilly, Dr. Cote, Dr. Ford, Dr. Novak, and Mr. Pauciulo have nothing to disclose.

Authors' contribution:
Sharp ME statistical analysis and drafting original manuscript; Caccappolo E analysis and interpretation, acquisition of data and critical revision of the manuscript for important intellectual content; Mejia-Santana H acquisition of data and critical revision of the manuscript for important intellectual content; Tang M-X acquisition of data, statistical analyses and critical revision of the manuscript for important intellectual content; Rosado L acquisition of data and critical revision of the manuscript for important intellectual content; Orbe Reilly M acquisition of data and critical revision of the manuscript for important intellectual content; Ruiz D acquisition of data and critical revision of the manuscript for important intellectual content; Louis ED acquisition of data and critical revision of the manuscript for important intellectual content; Comella C acquisition of data and critical revision of the manuscript for important intellectual content; Nance M acquisition of data and critical revision of the manuscript for important intellectual content; Bressman S acquisition of data and critical revision of the manuscript for important intellectual content; Scott WK acquisition of data and critical revision of the manuscript for important intellectual content and study funding; Tanner C acquisition of data and critical revision of the manuscript for important intellectual content; Waters C acquisition of data and critical revision of the manuscript for important intellectual content; Fahn S acquisition of data and critical revision of the manuscript for important intellectual content and study funding; acquisition of data and critical revision of the manuscript for important intellectual content; Cote L acquisition of data and critical revision of the manuscript for important intellectual content; Ford B acquisition of data and critical revision of the manuscript for important intellectual content; Rezak M acquisition of data and critical revision of the manuscript for important intellectual content; Novak K acquisition of data and critical revision of the manuscript for important intellectual content; Friedman JH acquisition of data and critical revision of the manuscript for important intellectual content; Pfeiffer R acquisition of data and critical revision of the manuscript for important intellectual content; Payami H acquisition of data and critical revision of the manuscript for important intellectual content and study funding; Molho E acquisition of data and critical revision of the manuscript for important intellectual content ; Factor S acquisition of data and critical revision of the manuscript for important intellectual content; Nutt J acquisition of data and critical revision of the manuscript for important intellectual content; Serrano C acquisition of data and critical revision of the manuscript for important intellectual content; Arroyo M acquisition of data and critical revision of the manuscript for important intellectual content. She also provided administrative, technical and material support; Pauciulo M acquisition of data and critical revision of the manuscript for important intellectual content; Nichols W acquisition of data and critical revision of the manuscript for important intellectual content; Clark L acquisition of data and critical revision of the manuscript for important intellectual content and study funding; Alcalay RN analysis and interpretation, statistical analysis, acquisition of data, drafting original manuscript and supervision. Marder K study concept and design, acquisition of data, analysis and interpretation, and drafting the manuscript, supervision and study funding.

[3]Gertrude H. Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[4]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

[5]Department of Neurological Sciences, Rush University Medical Center, Chicago, IL, USA6

[6]Struthers Parkinson's Center, Park Nicollet Clinic, Golden Valley, MN, USA

[7]The Alan and Barbara Mirken Department of Neurology, Beth Israel Medical Center, New York, New York, USA

[8]Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

[9]Dr. John T Macdonald Foundation, Department of Human Genetics, Miami Institute for Human Genomics, Miller School of Medicine, University of Miami, Miami, FL 33136, USA

[10]Parkinson's Institute, Sunnyvale, CA, San Francisco Veterans Affairs Medical Center and University of California-San Francisco, San Francisco, CA, UCA

[12]Central DuPage Hospital, Neurosciences Institute, Movement Disorders Center, Winfield, IL 60190

[13]Department of Neurology, at NorthShore University Health System, Evanston, Illinois, USA

[14]Department of Neurology, University of Chicago, Pritzker School of Medicine, Chicago, Illinois, USA

[15]Butler Hospital, Providence, Rhode Island, USA

[16]Department of Neurology, Alpert medical school of Brown University, Providence, Rhode Island, USA

[17]Department of Neurology, College of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, USA

[18]New York State Department of Health Wadsworth Center, Albany, NY, USA

[19]Parkinson's Disease and Movement Disorders Center of Albany Medical Center, Albany, NY

[20]Department of Neurology, Emory University, Atlanta, GA, USA

[21]Portland VA Medical Center Parkinson Disease Research, Education and Clinical Center, Portland, Oregon, USA and Oregon Health & Science University, Portland, Oregon, USA

[22]University of Puerto Rico, San Juan, Puerto Rico

[23]Division of Human Genetics, Cincinnati Children's Hospital Medical Center and the Department of Pediatrics; University of Cincinnati College of Medicine

[24]Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[25]Center for Human Genetics, College of Physicians and Surgeons, Columbia University, New York, NY, USA

[26]Department of Psychiatry, Columbia University Medical Center, NYC, NY, USA

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 that non-carriers suggesting that *PARKIN* heterozygosity may contribute to phenotype.

Keywords

Parkinson’s; neuropsychological; obsessive-compulsive; parkin

1. INTRODUCTION

Few studies have systematically investigated the association between *PARKIN* genotype and psychiatric co-morbidities of PD.[1–3] 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.[4] Obsessive-compulsive (OC) symptoms have been hypothetically linked to PD because both conditions involve the frontostriatal circuits.[5,6] 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).[7] *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.[8] 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.[9,10]

2. METHODS

2.1. Participants

Patients with EOPD defined by age at onset =< 50 years and their asymptomatic first degree relatives were recruited from 17 sites participating in the CORE PD study).[7,11] 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.[12–15] 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.[7,11] 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.[16] 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.[16] Higher scores indicate more symptoms. BDI-II scores for 88/104 probands and 218/257 relatives were previously reported.[4]

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 χ^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 $p \leq 0.10$ in bivariate analyses: depression (based on BDI>=15, an adjusted cutoff for diagnosis of depression)[17], language (English or Spanish), and in the asymptomatic relatives, mild cognitive impairment based on consensus diagnosis.[11] 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 ≥28 (i.e. severe depression)[18] 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,[1,2,7,19,20] *PARKIN* PD homozygotes or compound heterozygotes also have a distinctive non-motor symptom profile, which includes normal olfaction,[21] and less cognitive impairment.[11] 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.[22] Indeed, polymorphisms linked to OCD have been identified in genes related to serotonin, epinephrine and dopamine function.[23] 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.[8] 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.[9,10,24,25]

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’,[11,26] 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.[27]

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,[21] and Lewy bodies;[28,29] age at onset is younger in heterozygotes than non-carriers;[7] and asymptomatic heterozygotes have neuroimaging evidence of basal ganglia involvement.[9,10,24,25] 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);[16] though importantly, scores are not age-adjusted, an important consideration since OCS tend to decline throughout the lifespan.[30] Finally, we assume in our discussion that asymptomatic non-carriers have a normal dopaminergic system. However, because they are 1st 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.

Acknowledgments

ME Sharp and KS Marder had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The authors thank Drs. Paul Greene, Amy Colcher, Dana Jennings, Andrew Siderowf, Steven Frucht, Susan Mickel, and Ms. Linda Winfield for referral of participants.

Funding:

This study was funded by NIH NS036630, UL1 RR024156 (K.S.M.), NS050487, NS060113 (L.N.C.), K02NS080915 (R.N.A) the Parkinson's Disease Foundation (K.S.M., S.F., and L.N.C.), P50 NS039764 and P50 NS071674 (W.K.S) and NS36960 (H.P). The authors thank Drs. Paul Greene, Amy Colcher, Dana Jennings, Andrew Siderowf and Ms. Linda Winfield for referral of participants. Dr. Sharp had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dr. Louis receives research support from the NIH [NINDS #R01 NS42859 (principal investigator), NINDS #R01 NS39422 (principal investigator), #R01 NS08732 (principal investigator), #R01 NS085136 (principal investigator), #T32 NS07153-24 (principal investigator), #R01 NS36630 (co-Investigator)] and the Parkinson's Disease Foundation (principal investigator).

Dr. Comella serves on the editorial board of *Clinical Neuropharmacology* and *Continuum*. She receives research support from the NIH R01NS074343, U54NS065701, Dystonia Medical Research Foundation, Allergan Inc. Ipsen Biopharmaceuticals, Inc and Merz Pharmaceutical. She receives compensation/honoraria for services as a consultant or an advisory committee member: Allergan, Inc; Impax Pharmaceuticals; Ipsen Biopharmaceuticals,

Inc; Medtronic Inc.: Merz Pharmaceuticals; US World Meds.She receives royalties from Cambridge, Humana Press; Wolters Kluwer. She receives research support from the Parkinson's Disease Foundation.

Dr. Nance has received research funding from Medivation, Santhera, Neurosearch, Juvantia, Schwarcz, Pfizer, Neuraltus, Impax, CHDI, NINDS 5 U10 NS044466-05 (Site investigator), NINDS 5 RO1 NS36630 (Site investigator), NINDS NS640068-08 (Site investigator, Steering Committee), NHGRI/NINDS 501 HG 02449-07 (Site investigator), NINDS 1RO1 NS052592-01 (Site investigator), NCCAM (Site Investigator), 1 RO1 NS060118-01A1 (Site investigator); support for Centers of Excellence from National Parkinson Foundation and Huntington Disease Society of America; speaking honoraria from American Academy of Neurology, Huntington Disease Society of America, Medscape, and Augsburg College; and royalties from Oxford University Press (Juvenile Huntington's Disease, published 2009). She has participated on Advisory Boards for Lundbeck. Her spouse has served on speaker's bureaus for Genentech and Schering-Plough.

Dr. Bressman serves on the advisory boards of the Michael J. Fox Foundation, the Dystonia Medical Research Foundation, the Bachmann Strauss Dystonia and Parkinson's Foundation, and the Board of Directors of We Move. She has consulted for Bristol Meyer Squibb. She has received research support from the Michael J. Fox Foundation, and the National Institutes of Health (NIH). Dr. Bressman received royalty payments from Beth Israel/Mount Sinai/ Athena for DYT6 testing.

Dr. Scott is a co-inventor on patent regarding use of genetic data for assessing risk of developing age-related macular degeneration, licensed to ArcticDx, received speaking honoraria from CHDI, and received research support from the National Institutes of Health (EY023164; EY023194; AI068804; NS071674; EY012118; HG000026; AG019085), the BrightFocus Foundation, and the James & Esther King Biomedical Research Program.

Dr. Tanner serves on the Michael J. Fox Foundation Scientific Advisory Board and the National Spasmodic Dystonia Association Scientific Advisory Board. Has consulted for Adamas Pharmaceuticals, Impax Pharmaceuticals, Lundbeck Pharmaceuticals, Pacific Health Research Institute (consultant on NIH & Department of Defense-funded research), Stanford University (consultant on Muscular Dystrophy Association funded research) and SunHealth Research Institute (consultant on MJFF funded research). Has received research support from the Michael J. Fox Foundation, Brin Foundation, James and Sharron Clark, National Institutes of Health (NIH), Parkinson's Institute and Clinical Center, Parkinson's Disease Foundation, Department of Defense, Parkinson's Unity Walk and Welding Products Manufacturer's Group.

Dr. Waters received speaking honorarium from Teva and UCB. She receives research support from the Parkinson's Disease Foundation.

Dr. Fahn report receiving consulting and advisory board membership with honoraria from: Merz Pharma (Jan 2013), Genervon Biotechnology - expect to receive compensation serving as Principal Investigator of a pilot clinical trial. Grants/Research Support from the Parkinson's Disease Foundation (no salary support). Grant from the Smart Family Foundation (Dec. 2012). Lecture Honoraria: American Academy of Neurology (April 2012), Columbia University (July 2012), Sun Pharmaceuticals India (Nov 2012). Editor and Author Honoraria: Springer Publishers for serving as co-editor of Current Neurology and Neurosurgery Report (annual); Elsevier Publishers for co-authorship of book *Principles and Practice of Movement Disorders.*

Dr. Rezak is on the speaker bureau of Teva, Medtronic, Novartis, Boehringer Ingelheim, Galxo and UCB.

Dr. Friedman has received speaking honorarium from Teva, General Electric, UCB. He received research support MJFox; EMD Serono; Teva; Acadia; Schering Plough and the National Institute of Health. He has received consultation fee from Teva; Addex Pharm; UCB; Lundbeck; Roche. He has received book royalties from Demos press.

Dr. Pfeiffer reports receiving honoraria from CRC Press (Taylor & Francis); Humana Press. Lecture Honoraria from Teva, UCB, USWorldMeds. He received honoraria for consulting from Pfizer. Research Grant/Contracts: UCB. He is the journal editor of Parkinsonism and Related Disorders (Elsevier)

Dr. Payami has received funding from the NIH (NS36960).

Dr. Molho is supported by the Riley Family Chair in Parkinson's Disease. Has received consulting fees from US World Meds and Merz Pharmaceuticals. Has received research support from Merz Pharmaceuticals, Acadia Pharmaceuticals, Allergan, Prana Pharmaceuticals, Impax Pharmaceuticals, EMD Serono, NINDS # R01 NS060118 (site investigator), NIH #R01 NS050324-01A1 (site investigator).

Dr. Factor reports receiving honoraria from: Scientiae for CME program, University of Florida speaker program, Current Neurology and Neuroscience section editor, UpToDate. Consulting: Merz, Ipsen, Chelsea Therapeutics. Grants' support: Ceregene, Ipsen, EMD Serono, Allergan, Medtronics, Michael J. Fox Foundation, NIH. Royalties: Demos, Blackwell Futura for textbooks

Dr. Nutt reports receiving research support form the National Parkinson Foundation, NIH, Michael J. Fox foundation and Ceregene. He consults for Elan Pharmaceuticals, Lundbeck Inc., ONO Pharma, SynAgile Corp, Prexa Inc., US World Med. and Ceregen. He received speaking honoraria from the American Academy of Neurology

Dr. Serrano has received research funding from the Parkinson Study Group, Boehringer, TEVA, the MJF Foundation and the National Institutes of Health. Dr. Serrano has received speaker honorarium in the past from Boehringer and Allergan.

Dr. Arroyo reports receiving speakers' honorarium from UCB, Boehringer Ingelheim, Has received research founding from NIH, Pfizer and Pharmacia.

Dr. Nichols reports receiving support from the NIH/NHLBI (HL102107 (principal investigator) and HL105333(principal investigator)).

Dr. Clark receives research support from the NIH [NINDS #R01 NS060113 (principal investigator), NINDS #R01 NS073872 (Co-principal Investigator), NIA #5P50AG008702 (Project 3, principal investigator), and NINDS #NS36630 (co-investigator) and 2P50NS038370-11 (Co-Investigator)], and the Parkinson's Disease Foundation (principal investigator) and the Michael J Fox Foundation (co-investigator).

Dr. Alcalay receives research support from the NIH (K02NS080915), the Parkinson's Disease Foundation, the Smart Foundation and the Michael J Fox foundation.

Dr. Marder served on the editorial board of *Neurology*; receives research support from the NIH [NS036630 (PI), 1UL1 RR024156-01(Director PCIR), PO412196-G (Co-I), and PO412196-G (Co-I)]. She received compensation for participating on the steering committee for U01NS052592 and from the Parkinson Disease Foundation, Huntington's Disease Society of America, the Parkinson Study Group, CHDI, and the Michael J Fox foundation. She received honoraria from Pfizer and Springer SBM.

References

1. Lohmann E, Periquet M, Bonifati V, et al. How much phenotypic variation can be attributed to parkin genotype? Ann Neurol. 2003; 54:176–85. [PubMed: 12891670]
2. Khan NL, Graham E, Critchley P, et al. Parkin disease: a phenotypic study of a large case series. Brain. 2003; 126:1279–92. [PubMed: 12764051]
3. Kägi G, Klein C, Wood NW, et al. Nonmotor symptoms in Parkin gene-related parkinsonism. Mov Disord. 2010; 25:1279–84. [PubMed: 20629119]
4. Srivastava A, Tang M-X, Mejia-Santana H, et al. The relation between depression and parkin genotype: The CORE-PD study. Parkinsonism Relat Disord. 2011; 17:740–4. [PubMed: 21856206]
5. Anticevic A, Hu S, Zhang S, et al. Global Resting-State Functional Magnetic Resonance Imaging Analysis Identifies Frontal Cortex, Striatal, and Cerebellar Dysconnectivity in Obsessive-Compulsive Disorder. Biol Psychiatry. 2014; 75:595–605. [PubMed: 24314349]
6. Ahmari SE, Spellman T, Douglass NL, et al. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science. 2013; 340:1234–9. [PubMed: 23744948]
7. Marder K, Tang M-X, Mejia-Santana H, et al. Predictors of parkin mutations in early-onset Parkinson disease: the consortium on risk for early-onset Parkinson disease study. Arch Neurol. 2010; 67:731–8. [PubMed: 20558392]
8. Doherty KM, Silveira-Moriyama L, Parkkinen L, et al. Parkin Disease: A Clinicopathologic Entity? JAMA Neurol. 2013; 70:571–9. [PubMed: 23459986]
9. Hilker R, Klein C, Hedrich K, et al. The striatal dopaminergic deficit is dependent on the number of mutant alleles in a family with mutations in the parkin gene: evidence for enzymatic parkin function in humans. Neurosci Lett. 2002; 323:50–4. [PubMed: 11911988]
10. Hilker R, Klein C, Ghaemi M, et al. Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the parkin gene. Ann Neurol. 2001; 49:367–76. [PubMed: 11261512]
11. Alcalay RN, Caccappolo E, Mejia-Santana H, et al. Cognitive and Motor Function in Long-Duration PARKIN-Associated Parkinson Disease. JAMA Neurol. 2014; 71:62–7. [PubMed: 24190026]

12. Alcalay RN, Mejia-Santana H, Tang M-X, et al. Self-report of cognitive impairment and mini-mental state examination performance in PRKN, LRRK2, and GBA carriers with early onset Parkinson's disease. J Clin Exp Neuropsychol. 2010; 32:775–9. [PubMed: 20182943]
13. Clark LN, Haamer E, Mejia-Santana H, et al. Construction and validation of a Parkinson's disease mutation genotyping array for the Parkin gene. Mov Disord. 2007; 22:932–7. [PubMed: 17415800]
14. Clark LN, Afridi S, Karlins E, et al. Case-control study of the parkin gene in early-onset Parkinson disease. Arch Neurol. 2006; 63:548–52. [PubMed: 16606767]
15. Pankratz N, Kissell DK, Pauciulo MW, et al. Parkin dosage mutations have greater pathogenicity in familial PD than simple sequence mutations. Neurology. 2009; 73:279–86. [PubMed: 19636047]
16. Watson D, Wu KD. Development and validation of the Schedule of Compulsions, Obsessions, and Pathological Impulses (SCOPI). Assessment. 2005; 12:50–65. [PubMed: 15695743]
17. Visser M, Leentjens AFG, Marinus J, Stiggelbout AM, van Hilten JJ. Reliability and validity of the Beck depression inventory in patients with Parkinson's disease. Mov Disord. 2006; 21:668–72. [PubMed: 16450355]
18. Beck, AT.; Steer, RA.; Brown, G. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
19. Lohmann E, Thobois S, Lesage S, et al. A multidisciplinary study of patients with early-onset PD with and without parkin mutations. Neurology. 2009; 72:110–6. [PubMed: 18987353]
20. Ishikawa A, Tsuji S. Clinical analysis of 17 patients in 12 Japanese families with autosomal-recessive type juvenile parkinsonism. Neurology. 1996; 47:160–6. [PubMed: 8710071]
21. Alcalay RN, Siderowf A, Ottman R, et al. Olfaction in Parkin heterozygotes and compound heterozygotes: the CORE-PD study. Neurology. 2011; 76:319–26. [PubMed: 21205674]
22. Graybiel AM, Rauch SL. Toward a neurobiology of obsessive-compulsive disorder. Neuron. 2000; 28:343–7. [PubMed: 11144344]
23. Stewart SE, Yu D, Scharf JM, et al. Genome-wide association study of obsessive-compulsive disorder. Mol Psychiatry. 2013; 18:788–98. [PubMed: 22889921]
24. Buhmann C, Binkofski F, Klein C, et al. Motor reorganization in asymptomatic carriers of a single mutant Parkin allele: a human model for presymptomatic parkinsonism. Brain. 2005; 128:2281–90. [PubMed: 15947065]
25. Binkofski F, Reetz K, Gaser C, et al. Morphometric fingerprint of asymptomatic Parkin and PINK1 mutation carriers in the basal ganglia. Neurology. 2007; 69:842–50. [PubMed: 17724286]
26. Ahlskog JE. Parkin and PINK1 parkinsonism may represent nigral mitochondrial cytopathies distinct from Lewy body Parkinson's disease. Parkinsonism Relat Disord. 2009; 15:721–7. [PubMed: 19815446]
27. Beglinger LJ, Paulsen JS, Watson DB, et al. Obsessive and compulsive symptoms in prediagnosed Huntington's disease. J Clin Psychiatry. 2008; 69:1758–65. [PubMed: 19012814]
28. Ruffmann C, Zini M, Goldwurm S, et al. Lewy body pathology and typical Parkinson disease in a patient with a heterozygous (R275W) mutation in the Parkin gene (PARK2). Acta Neuropathol (Berl). 2012; 123:901–3. [PubMed: 22555654]
29. Sharp ME, Marder KS, Cote L, et al. Parkinson's disease with Lewy bodies associated with a heterozygous PARKIN dosage mutation. Mov Disord. 2014; 29:566–8. [PubMed: 24375549]
30. Balsis S, Gleason MEJ, Woods CM, Oltmanns TF. An item response theory analysis of DSM-IV personality disorder criteria across younger and older age groups. Psychol Aging. 2007; 22:171–85. [PubMed: 17385993]

Table 1

Demographic and clinical characteristics of probands and asymptomatic 1st degree relatives by *PARKIN* genotype

	PD probands				Asymptomatic relatives			
Characteristic	**Non-carriers n=55**	**1 *PARKIN* mutation n=23**	**2 *PARKIN* mutations n=26**	**p-value#**	**Non-carriers n=171**	**1 *PARKIN* mutation n=80**	**2 *PARKIN* 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)[a]	15.7 (2.7)[a]	13.5 (3.4)[b]	0.02	14.4 (2.9)	14.5 (3.0)	13.8 (2.0)	0.88
Disease duration (years)	11.8 (6.1)[a]	13.7 (7.2)[a]	21.4 (11.0)[b]	<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)*	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)[a]	9.8 (7.7)[b]	0.02
Depressed (BDI>= 15) (%)	31.5	21.7	29.2	0.69	8.4	5.0[a]	33.3[b]	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
SCOPI total (sum 5 items)	56.4 (28.0)	43.3 (26.3)	40.9 (29.8)	0.04	45.5 (27.6)[a]	54.4 (26.3)[b]	69.2 (28.4)	0.01
SCOPI OCD (sum 1st 3 items)	45.1 (22.1)[a]	34.8 (21.6)	31.8 (24.3)[b]	0.03	36.9 (22.7)[a]	44.2 (21.6)[b]	59.3 (27.8)[b]	0.01
Obsessive Checking	18.8 (11.9)[a]	11.7 (10.2)[b]	11.2 (10.8)[b]	0.01	13.4 (10.6)[a]	16.2 (11.4)[a]	23.7 (9.5) [b]	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)[a]	8.6 (6.3)	5.2 (5.7)[b]	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. SCOPI-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[27]

Table 2

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

	PD probands			Asymptomatic relatives		
SCOPI-OCD score		**Mean difference in SCOPI OCD score compared to non-carriers (95% CI) p-value**			**Mean difference in SCOPI OCD score compared to non-carriers (95% CI) p-value**	
	Non-carriers	***PARKIN* 1 mutation**	***PARKIN* 2 mutations**	**Non-carriers**	***PARKIN* 1 mutation**	***PARKIN* 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.

Mov Disord. Author manuscript; available in PMC 2016 February 01.