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The relation between depression and parkin genotype:the CORE-PD Study

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Abstract

Background—Mutations in parkin are a known genetic risk factor for early-onset Parkinson's disease (EOPD) but their role in non-motor manifestations is not well established. Genetic factors for depression are similarly not well characterized. We investigate the role of parkin mutations in depression among those with EOPD and their relatives.

Methods—We collected psychiatric information using the Patient Health Questionnaire and Beck Depression Inventory II on 328 genotyped individuals including 88 probands with early onset PD (41 with parkin mutations, 47 without) and 240 first and second degree relatives without PD.

Results—Genotype was not associated with depression risk among probands. Among unaffected relatives of EOPD cases, only compound heterozygotes (n=4), and not heterozygotes, had significantly increased risk of depressed mood (OR=14.1; 95% CI 1.2–163.4), moderate to severe depression (OR=17.8; 95% CI 1.0–332.0), depression (score ≥15) on the Beck Depression Inventory II (BDI-II) (OR=51.9; 95% CI 4.1–657.4), and BDI-II total depression score (β =8.4; 95% CI 2.4–11.3) compared to those without parkin mutations.

Conclusions—Relatives of EOPD cases with compound heterozygous mutations and without diagnosed PD may have a higher risk of depression compared to relatives without parkin mutations. These findings support evidence of a genetic contribution to depression and may extend the phenotypic spectrum of parkin mutations to include non-motor manifestations that precede the development of PD.

Article keywords

genetics; depression; parkin; Parkinson's disease; neuropsychiatry; early onset Parkinson's disease

Introduction

Depression is a very common non-motor symptom of Parkinson's disease (PD), occurring in approximately 40% of patients [1], though it remains under recognized. Early onset PD (EOPD), commonly defined as PD with onset <50 years of age, has been associated with greater occurrence of depression relative to older onset PD despite similar disease severity or disability [2]. Psychiatric disorders, including depression and anxiety, may precede the motor manifestations of Parkinson's disease by years [3]. Mutations in the parkin gene (PARK2) on chromosome 6q have been implicated in early onset PD with a possible autosomal recessive mode of inheritance [4]. One study found an increased risk of depression and anxiety among patients with PD and their relatives, particularly among those with EOPD [5]. Parkin genotype has been explored for its association with age at onset (AAO), the Mini-Mental State Examination (MMSE), and Unified Parkinson's Disease Rating Scale (UPDRS) motor scores [6], but to our knowledge only two other studies [7,8] have investigated genotype with respect to psychiatric features. Neither study found an association between parkin genotype and depression.

We sought to determine the relation between depression, as evaluated by two instruments, the Patient Health Questionnaire [9] and the Beck Depression Inventory II (BDI-II) [10], and genotype in a family-based sample of probands with EOPD and their relatives. The finding of a genetic contributor to depression in EOPD or those at risk could be of value in the understanding of both depression and EOPD. Characterization of the parkin phenotype might suggest management approaches, including surveillance.

Methods and Materials

Study design and statistical analysis

Probands with an age at onset of PD ≤ 50 years were recruited from 1998 to 2003 at Columbia University as part of the Genetic Epidemiology of PD study (GEPD) (n=247) and from 2004 through 2009 at 13 participating centers as part of the Consortium on Risk For Early-Onset PD (CORE-PD) study (n=709) [11]. A detailed description of probands including mutations is outlined elsewhere [11] as are methods of the GEPD study [12]. Institutional review board approval was obtained at all participating sites and each subject signed informed consent. The presence of two of four signs of bradykinesia, rest tremor, muscular rigidity, or postural instability, with at least one being either bradykinesia or rest tremor, was necessary for the diagnosis of PD [13]. Exclusion criteria included secondary parkinsonism, Parkinson plus syndromes, dementia with Lewy Bodies or dementia predating motor symptoms.

Initial CORE-PD assessment (Part I) included demographic information, the Unified Parkinson's Disease Rating Scale (UPDRS) [14], a validated family history interview, and a blood sample from which DNA was isolated. In Part II of the study we attempted to contact, without revealing mutation status, all probands who carried parkin mutations and a subset of probands who did not carry parkin mutations. Consent was obtained for further evaluation of each proband and his or her first-degree relatives ≥ 18 years. Part II evaluation [11] expanded on the above to include a neuropsychological evaluation and a detailed psychiatric assessment as described below. Further expansion of families beyond first-degree relatives was performed using the same assessments if the relative had a diagnosis of Parkinson's disease or carried a parkin mutation. Columbia University staff conducted in-person examinations without knowledge of mutation status.

Depression was assessed with two instruments. The Patient Health Questionnaire (PHQ) of the Primary Care Evaluation of Mental Disorders (PRIME-MD) is a self-assessment tool that assesses depressive, anxiety, alcohol, somatoform, and eating disorders [15]. The PHQ-9, the depression component of the PHQ, consists of nine items scored on a three point scale (0="not at all"; 1="several days"; 2="more than half the days"; 3="nearly every day") and is well validated against Diagnostic Statistical Manual IV (DSM-IV) depression criteria [9]. Major depression was diagnosed if during the preceding two week period subjects endorsed either "feeling down..." or experiencing "little interest or pleasure in doing things", "more than half the days", and further endorsed items including decreased energy or difficulty sleeping to total five or more of nine symptoms. Past history of major depression is not part of the original PHQ but was solicited for this study. Responses to depressive symptoms for past history could only be binary ("yes" or "no") but categorization was otherwise performed as above for current depression.

Several regression analyses were conducted with the results of the PHQ as the outcome. In the first, the dependent variable was major depression, modeled as a dichotomous outcome. In the second logistic regression, because depressed mood may be of clinical importance [16] independent of a diagnosis of major depression, depressed mood (first item of the PHQ-9 major depression subscale) "several days" to "nearly every day" was the dependent

variable. Because depression in PD may be mild [17] we also performed multinomial regression to examine severity of depressive symptoms. 'No depression', 'mild', 'moderate', 'moderate-severe', and 'severe depression' were categorized using total score cut points of 5, 10, 15, and 20 respectively [9]. Moderate and severe depression was collapsed into one category because of limited sample size.

The BDI-II is a self-report inventory validated for use in Parkinson's patients [18] in which each of 21 items is scored on a four-point scale [10]. In contrast to the PHQ-9, the BDI-II includes a cognitive inquiry of pessimism and self-blame, for example, in addition to somatic items such as diminished libido.

Based on previous work in PD [19], those scoring 15 or higher were classified as depressed and this dichotomous outcome was modeled in a logistic regression, as was BDI-II total score in a linear regression.

We also explored the effects of a number of covariates, including a past history of major depression, sex, marital status (single vs. currently married), race (self identification as either non-Hispanic White, Hispanic, non-Hispanic Black, or Other), age, and current antidepressant use. Among subjects with PD, disease severity (as assessed by summed UPDRS Part I&II, and Part III total scores) and duration were modelled separately as continuous variables. Tremor dominant and postural-instability gait disorder categorization was also considered for inclusion as a covariate [20].

Covariates were explored with dependent variables to examine for the presence of zero cells; 'African American' and 'Others' were excluded on this basis and elsewhere variables were collapsed as appropriate. Because the prevalence of depression is higher among subjects with versus without PD [1], we performed separate analyses in probands and relatives. We also excluded from the analysis seven relatives diagnosed with PD. For analysis of depression in the relatives, we used backwards-stepwise regression with Generalized Estimating Equations (GEE) to account for familial correlations. We performed separate analyses of all first-degree and second-degree relatives, and first-degree relatives only.

Any covariates associated with depressed mood at $p \leq 0.10$ in bivariate analysis were included in subsequent regression models. Subjects with missing values on any of the variables in the model were excluded. After performing initial analyses, we repeated the analysis with several exclusions: probands and their families with the G2019S mutation in the leucine-rich repeat kinase (LRRK2) gene ($n=4$) or with beta glucocerebrosidase (GBA) mutations N370S ($n=12$) and L444P ($n=5$), and subjects with any form of bipolar disorder ($n=5$). Because of statistical considerations as above, those self-reporting as African American ($n=5$; 4 relatives, 1 proband) or 'Other' ($n=11$; 6 relatives, 5 probands) race were excluded.

Molecular Methods

All subjects were screened for sequence variants with denaturing high performance liquid chromatography (DHPLC) and either a parkin genotyping array or, for 126 subjects, direct sequencing. All exons and exon-intron boundaries of the parkin gene were sequenced. Semi-quantitative multiplex PCR approach was performed on all samples to evaluate gene dosage and mutations including exon deletions, duplications, and multiplications. Further methodological details are outlined elsewhere [11].

Results

The sample included 328 individuals (88 probands and 240 relatives) with both genotyping and psychiatric information. Among the 240 relatives, 218 were first-degree (40 parents, 100 siblings, 78 children) and 22 second-degree. Stratification by genotype and disease status is displayed in Tables 1 and 2.

Among the probands, compound heterozygotes (n=16) and homozygotes (n=4) had significantly earlier age at onset and longer disease duration compared with the other two groups (heterozygotes and subjects with no mutations) (Table 1). However, adjusted for the only significant covariate to emerge in a backward step-wise approach i.e. past history of major depression, genotype status was not associated with any depression outcome (data not shown).

Among all relatives, the proportion with depressed mood (first item of the PHQ-9) as well as both Beck depression (cut-off ≥ 15) and mean total Beck II score differed significantly by genotype (Table 2). Regression analysis revealed no significant association with any outcome among all genotypes combined (heterozygotes and compound heterozygotes), or heterozygotes only compared with subjects with no mutations (data not shown). There were no homozygote relatives in the sample.

Among four compound heterozygotes (in three families, all first-degree), however, we observed an association with several depression measures: depressed mood, moderate-severe depression on the PHQ, and both depression (score ≥ 15) and total score on the Beck Depression Inventory (Table 3). None of the relatives with two mutations had major depression (Table 2). Analysis of only first-degree relatives resulted in similar point estimates and significance (Table 3). Among both probands and relatives, removal of those with the LRRK2 and GBA mutations did not significantly alter our findings (data not shown). No clear pattern of mutations was observed by depression status among compound heterozygotes (Table 4).

Discussion

Because of previous reports of an association between EOPD and depression and the demonstrated non-motor signs such as cognitive impairment among mutation-carrying subjects in other diseases such as Huntington disease [21], we hypothesized that those with parkin mutations might be predisposed to depression prior to the onset of PD. Among relatives of EOPD cases, we observed a significantly increased risk of depression outcomes in a small number of subjects with compound heterozygote, but not heterozygote, mutations. None of the four compound heterozygotes had major depression. In contrast, we did not find a positive association of depression with genotype among EOPD probands, although they had a relatively high prevalence of depression, with almost half (46.6%) indicating depressed mood for at least some days to a week over the last two weeks.

Few previous studies have assessed the genetics of depression in EOPD. Arabia et al. [5] noted a significantly increased risk of depressive disorders among first-degree relatives – parents and siblings (but not offspring) of patients with PD compared with relatives of controls, particularly among relatives of patients with a younger age (≤ 66 years) at PD onset. Genotyping was not performed. In contrast, the two studies that examined depression by parkin genotype status have not observed a significant association. Lohmann et al.'s study [7] of 44 patients, all with early onset (≤ 45 years) PD, approximately half with homozygous (n=2) or compound heterozygous (n=19) parkin mutations, found no significant differences by genotype including depression as measured principally by the Montgomery Asberg Depression Rating Scale (MADRS) and Mini International

Neuropsychiatric Interview (MINI). Pankratz et al., using the Geriatric Depression Rating Scale (GDS), similarly observed no significant association with depression in a sibling pair study [8]. These studies are difficult to compare because of differences in rating scales and ages of onset: the Geriatric Depression Rating Scale (GDS) and an age of onset of <60 [8]; the MADRS and MINI and age of onset of <45 [7]; and DSM-IV criteria and age of onset of <66 [5].

Major depression was not associated with genotype. It is unclear why this was so but different measures of depression may also be valid. Depression in PD in a community sample, for instance, was evaluated using a number of different measures [22]; whereas the prevalence of major depression by DSM-III criteria was 7.7%, 24.1% of patients had a BDI score of 18 or more “indicating clinically relevant depressive symptoms”, and 45.5% of all patients had a mild grade of depressive symptoms by the MADRS. It is possible then that depression among those with or at risk of PD may be represented by outcomes other than major depression, such as depressed mood. Consideration to a broader interpretation of depression among those with PD has been suggested [23].

There may be shared expression of PD symptoms and the somatic items of depression scales including the BDI [19]. Inclusive approaches to depression have however been suggested [24] and consequently we did not attempt to classify symptoms by presumed etiology. The use of a diagnostic psychiatric interview in our study might have yielded different estimates of depression outcomes.

We observed a significant association between parkin genotype and depression in a small subset of compound heterozygote relatives who did not meet criteria for PD. Because estimates of the penetrance of parkin mutations are imprecise [25] it remains uncertain how many of the relatives in our study will ultimately develop motoric features. Epidemiological and biological evidence support our findings. In one study [26] of late onset PD, 9.2% of patients had a history of depression at the time of a diagnosis of PD, compared with 4% of the control population. In a study of an Irish family kindred, Khan et al. observed dopaminergic dysfunction in the caudate and putamen measured by [¹⁸F]-dopa among four subjects with heterozygous parkin mutations, all of whom were asymptomatic [27]. Degeneration of dopaminergic fibers, especially those arising from the ventral tegmental area, has been suggested to be involved in depression [23]. Parkin knockout mice with the exon 7 deletion exhibit cell loss in the locus coeruleus [28] where such loss is postulated to be developmental rather than age-related. The locus coeruleus is a primary noradrenergic output and there is evidence that noradrenaline may be involved in depression [29].

The lack of association between parkin mutations and depression among cases with EOPD is unexplained. The higher overall prevalence of depression among EOPD patients may mask the contribution of parkin genotype. The contribution of parkin mutations to depression, relative to other psychosocial and genetic causes, might be greater earlier in the course of the disease. We did not however observe an association in probands between parkin mutation status and either past history of major depression or past depressed mood; with respect to the influence of other genetic modifiers, exclusion of common LRRK2 and GBA mutations did not alter results.

We did not find an association among heterozygotes in either probands or relatives. The pathogenicity of parkin heterozygosity is unclear but heterozygotes may have a later age of PD onset than homozygotes or compound heterozygotes [30]. The presence of such a dose effect would be consistent with our finding of a lack of an association of heterozygosity with depression. Location and type of mutation may affect phenotype [30] though we found no clear association with mutation based on a small number of compound heterozygotes.

Our findings are derived from a small subset of subjects and need to be confirmed in a larger sample. Nonetheless, the findings were significant and biologically plausible. The association is further observable across a variety of measures. If confirmed, these findings relating to genotype-phenotype correlation in EOPD may guide surveillance for psychiatric disorders among those at risk. Longitudinal follow-up of depressed subjects without PD but with compound heterozygote parkin mutations might reveal whether such subjects have altered risk of developing PD. Future studies of parkin mutations could improve understanding of the etiology of both PD and depression.

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Table 1

Demographic and clinical characteristics among probands by parkin genotype

	All probands (n=88)	No parkin mutations (n=47)	Heterozygotes (n=21)	Homozygotes and compound heterozygotes (n=20)
Age, mean yrs (s.d.)	52.8 (8.8)	53.8 (7.6)	51.9 (7.0)	51.7 (12.4)
Age at onset (sd) *	38.3 (9.4)	42.4 (5.9)	37.8 (9.3)	29.1 (9.7)
Disease duration *, years (s.d.)	14.6 (8.6)	11.4 (5.4)	14.0(6.7)	22.7 (11.4)
Male sex (%)	59.1	59.6	61.9	55.0
Married (%)	77.3	80.9	81.0	65.0
Hispanic (%)	15.9	10.6	14.3	30.0
Major depression ^ (%)	8.0	10.6	9.5	0.0
Moderate-severe depression ^ (%)	25.0	29.8	23.8	15.0
Mild depression ^ (%)	33.0	34.0	23.8	40.0
Depressed mood ^^ (%)	48.9	48.9	33.3	55.0
Mean BDI score (s.d.)	10.2 (7.7)	10.9 (8.6)	9.8 (6.7)	9.1 (6.6)
Depression by BDI cut-off ≥ 15 (%)	26.8	25.6	23.8	33.3
Current antidepressant use ** (%)	30.7	34.0	33.3	20.0
Past history of major depression (%)	43.7	50.0	33.3	40.0
UPDRS Part I&II score(s.d.)	16.7 (7.8)	18.0 (8.4)	15.0 (7.8)	15.4 (6.3)
UPDRS Part III score (s.d)	20.8 (7.5)	20.5 (8.1)	20.8 (7.6)	18.7 (6.9)
Postural-instability gait disorder (%)	61.4	55.3	66.7	70.0

* Groups significantly ($p \leq 0.05$) different by chi-square or F-test

** Includes SSRI's (e.g. citalopram), bupropion, venlafaxine, monoamine oxidase inhibitors, and tricyclics

^ Based on PHQ; mild depression PHQ-9 depression score of 5–9; moderate depression PHQ-9 depression score of ≥ 10 ; major depression as defined in text

^^ Single item of the PHQ-9 (“Feeling down, depressed, or hopeless” at least “several days” over the last two weeks)

Table 2

Demographic and clinical characteristics among first and second degree relatives by parkin genotype

	All relatives (n=240)	No parkin mutations (n=164)	Heterozygotes (n=72)	Compound heterozygotes [#] (n=4)
Age, mean years (s.d)	46.7 (18.8)	47.5 (18.5)	45.3 (19.8)	38.5 (12.6)
Male Sex (%)	38.3	62.2	63.9	25.0
Married (%)	62.1	62.2	63.9	25.0
Hispanic (%)	13.3	13.4	13.9	0.0
Major depression (%) [^]	5.0	6.7	1.4	0.0
Moderate to severe depression [^] (%)	10.4	12.2	5.6	25.0
Mild depression [^] (%)	15.8	16.5	12.5	50.0
Depressed mood ^{^^} (%)	26.3	27.4	20.8	75.0
Mean BDI-II score [*] (s.d.)	5.0 (6.0)	5.3 (6.2)	3.9 (5.2)	12.3 (6.4)
Depression by BDI-II cut-off ≥ 15 [*] (%)	8.6	8.9	5.6	50.0
Current antidepressant use ^{**} (%)	7.5	7.3	6.9	25.0
Past history of major depression [^] (%)	19.2	22.7	12.5	0.0

* Groups significantly ($p \leq 0.05$) different by chi-square or F-test

** Includes SSRI's (e.\italopram), bupropion, venlafaxine, monoamine oxidase inhibitors, and tricyclics

[#] No homozygotes were present among those without PD

[^] Based on PHQ; mild depression PHQ-9 depression score of 5–9; moderate depression PHQ-9 depression score of ≥ 10 ; major depression as defined in text

^{^^} Single item of the PHQ-9 (“Feeling down, depressed, or hopeless” at least “several days” over the last two weeks)

Table 3

Odds ratio* or parameter estimate^a and 95% confidence intervals for outcomes among compound heterozygotes (all relatives and first degree relatives only)

	Odds ratio or parameter estimate (95% CI)		Odds ratio or parameter estimate (95% CI)	
	All relatives	p value	First degree relatives	p value
Depressed mood [^]	14.1 (1.2,163.4)	0.03	13.4 (1.2,156.3)	0.04
Depression by BDI-II cut-off ≥ 15	51.9 (4.1,657.4)	0.00	38.5 (3.4,443.7)	0.00
BDI-II Total score ^a	8.4 (2.4,14.3)	0.00	8.0 (2.1,13.9)	0.00
Major depression ^{^^}	0 (0,infinity) ^b	-	0 (0,infinity) ^b	-
PHQ Depression severity				
Mild ^{^^}	8.4 (0.7,93.1)	0.08	7.5 (0.7,85.1)	0.10
Moderate- severe ^{^^}	17.8 (1.0,332.0)	0.05	18.2 (1.0,336.5)	0.05

* Relative to parkin wild-type, adjusted for antidepressant use, race [Hispanic vs. White], and past history of major depression

^aBDI Total score (linear regression)

^bNo compound heterozygotes with major depression

[^]Single item of the PHQ-9 ("Feeling down, depressed, or hopeless" at least "several days" over the last two weeks)

^{^^}Based on PHQ; mild depression PHQ-9 depression score of 5–9; moderate depression PHQ-9 depression score of ≥ 10 ; major depression as defined in text

Table 4

Familial relationship, ethnicity, and genotype among compound heterozygotes by depression status

Depression status of relative	Relationship to proband	Ethnicity	Genotype
Depressed mood [^]	Sibling	White	Exon 3 40bp del/Arg275Trp
	Sibling [*]	White	202-3delAG/del exon 3–4
	Sibling [*]	White	202-3delAG/del exon 3–4
No depressed mood	Child	White	202-3delAG/Arg275Trp

[^] Depressed mood (first item of the PHQ-9 major depression subscale) “several days” to “nearly every day”

^{*} Members of same family