Published in final edited form as:

Int J Neurosci. 2013 December ; 123(12): 847–849. doi:10.3109/00207454.2013.810626.

Variability in clinical phenotypes of heterozygous and homozygous cases of *Parkin*-related Parkinson's disease

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Abstract

Parkin mutations are a common cause of early-onset Parkinson's disease. To study the clinical features and treatment responses of patients with homozygous or heterozygous *Parkin* mutations, we performed a retrospective chart review in six early-onset parkinsonism patients with pathogenic *Parkin* mutations. The clinical phenotypes observed in this cohort, all drawn from different families, were variable. All patients had a slowly progressive form of parkinsonism that responded well to dopaminergic therapy with the exception of one advanced case. Homozygous patients had an earlier age at disease onset than heterozygous patients. Two of our patients underwent bilateral deep brain stimulation (DBS) of the subthalamic nucleus or globus pallidus leading to a sustained positive response. Our observations support an earlier age of onset for homozygous cases and possible beneficial effects of DBS in *Parkin*-related parkinsonism.

Introduction

Parkin is a 465 amino acid protein located at what has been referred to as the PARK 2 locus on the long arm of chromosome six [1]. *Parkin* is widely expressed throughout the brain and functions as an ubiquitin ligase that attaches ubiquitin molecules to misfolded proteins in order to flag them for proteasomal processing [2]. This system is thought to be important in protein degradation and later deposition of alpha-synuclein into brain tissue [2].

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Declaration of Interest

The authors alone are responsible for the content and writing of the article. Dr. Okun serves as a consultant for the National Parkinson Foundation, and has received research grants from NIH, NPF, the Michael J. Fox Foundation, the Parkinson Alliance, Smallwood Foundation, and the UF Foundation. Dr. Okun has previously received honoraria, but in the past >36 months has received no support from industry including travel. Dr. Okun has received royalties for publications with Demos, Manson, and Cambridge (movement disorders books). Dr. Okun has participated in CME activities on movement disorders sponsored by the USF CME office, PeerView, and by Vanderbilt University. The institution and not Dr. Okun receives grants from Medtronic and ANS/St. Jude, and the PI has no financial interest in these grants. Dr. Okun has participated as a site PI and/or co-I for several NIH, foundation, and industry sponsored trials over the years but has not received honoraria.

Mutations within the *Parkin* gene are known to cause early-onset Parkinson's disease (EOPD), particularly in patients who develop symptoms prior to the age of 40 [3]. The exact pathogenic mechanism that leads to clinical symptoms remains unknown, but is thought to involve loss of ubiquitin ligase activity. Deletions, point mutations and duplications have all been identified in *Parkin* mutation carriers.

The clinical phenotype associated with *Parkin* mutations includes levodopa-responsive parkinsonism with the presence of diurnal fluctuations, dystonia and levodopa-induced motor fluctuations [4]. Although phenotype–genotype connections have yet to be established, there has been speculation that the type of mutation (heterozygote, compound heterozygote, homozygote) may influence the clinical picture, and the treatment outcome. Here, we report on the clinical features and therapeutic responses of six *Parkin*-related parkinsonism patients followed in our clinical cohort.

Methods

Genetic analysis of *Parkin*

Previously, our collaborative research group performed a mutation screening study in which we screened EOPD samples and normal controls from the NINDS biorepository at the Coriell Institute for Medical Research (<http://www.coriell.org/>). We examined samples for sequence and copy number mutations associated with *Parkin*. Detailed methods and results of this screening study have been published elsewhere [5]. Briefly, 13 PD patients carrying pathogenic mutations were identified in this study, and five had been followed by the University of Florida Movement Disorders clinic. We therefore undertook a retrospective chart review of these five individuals to examine the clinical phenotype and treatment responses. During the chart review and database review, we further identified an additional EOPD patient with a pathogenic *Parkin* mutation. This patient's mutation status was determined using commercial testing (Athena Diagnostics, Worcester, MA, USA), and we included this patient in the current study.

Clinical analysis

All patients were diagnosed by movement disorders specialists at the University of Florida Center for Movement Disorders & Neurorestoration. For each patient, all of the neurological notes were analyzed for medication use, Unified Parkinson's Disease Rating Scale Scores (UPDRS), PD subtype, age at symptom onset and other clinical features. Inclusion criteria were: patients over the age of 18, clinical diagnosis of PD and possessing laboratory documentation of either homozygous or heterozygous *Parkin* mutations. Written informed consent was obtained for each individual, and the study was approved by the institutional review board.

Results

Identified were six PD patients with mutations in *Parkin*, of whom two were homozygous and four heterozygous mutation carriers. Table 1 summarizes the clinical features of each patient.

The mean age at diagnosis was 50 for the heterozygotes and 28 for the homozygotes. There was one female heterozygote and one female homozygote. The PD subtypes varied throughout the group and included patients with both tremor predominant and akinetic rigid subtypes of PD. The on/off medication scores also varied between remarkable improvements of greater than 50% change in the UPDRS III score to a less than 15% improvement with dopaminergic therapy. Disease duration and UPDRS subscores were also markedly varied between the identified *Parkin* patients, and especially between the heterozygous patients. One heterozygous patient had an on-medication score that was not available; otherwise, all of the patients had improvement in UPDRS III scores in the on-medication state.

One of the most striking differences between homozygotes and heterozygotes was the age of onset of symptoms. Both of the homozygotes were affected during the third decade, which was approximately 20 years prior to the heterozygote onset. The homozygotes had marked dyskinesias, and both underwent deep brain stimulation (DBS) (one patient received bilateral pallidal stimulators and the other received bilateral subthalamic stimulators).

The subtype of PD varied between tremor predominant and akinetic rigid without a clearly dominant phenotype. Five of the six patients had various psychiatric symptoms or syndromes including anxiety, depression, bipolar disorder, hypersexuality (not on a dopamine agonist), personality disorder, narcotic addiction and previous, non-DBS-related suicide attempts. On examination, the cohort of homozygotes and heterozygotes had improvement of UDPRS score following administration of levodopa.

Discussion

The *Parkin* patients in this cohort all from different families, had variable clinical presentations and different ages of onset. There was no definite clinical picture that distinguished homozygous from heterozygous *Parkin*-related PD, with the exception of an earlier age at onset for homozygous cases. It is possible, therefore, that a heterozygous *Parkin* mutation may not contribute, as much as one might expect, to the clinical phenotype of PD; however, more cases will be needed to clarify this issue.

Previous research has suggested that patients with *Parkin* mutations respond reasonably well to DBS of the subthalamic nucleus [6,7]. In support of this previously reported observation, both of the homozygous *Parkin* mutation carriers had a pronounced and lasting response to DBS, one in the subthalamic nucleus and one in the globus pallidus. Our patient with GPi DBS was implanted mainly for suppression of dyskinesias, and he has experienced a long-term benefit for more than eight years. This patient had advanced disease by the time he was implanted and this may have accounted for the low on–off UPDRS improvement. Our patient with STN DBS has had a robust and sustained improvement for greater than three years of clinical follow-up.

In summary, the clinical presentation of *Parkin*-related Parkinson's disease in this small cohort of patients revealed disease onset before the age of 40, marked response to levodopa, early dyskinesias, the presence of dystonia and excellent response to DBS. There was an

earlier age of onset for homozygous cases. None of our patients expired, so we could not confirm the absence of Lewy body pathology which is classic in *Parkin* cases. Though the sample size was small, the heterogeneity in patients proved remarkable and some what unexpected. As larger *Parkin* databases emerge, it will be interesting to see if these observations will be consistent.

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Table 1

PARKIN cases: Clinical Cases and Treatment Responses.

Patient ID	Parkin mutation	AAO	Clinical description	Treatment response	UPDRS OFF/ON medication
ND01119 ^a	Heterozygous (deletion exon 2)	47	Tremor predominant; Medication refractory tremor	responsive to L-DOPA	48/unavailable
ND01122 ^a	Heterozygous (p.R275W)	46	Akinetic rigid; Marked anxiety; non-motor symptoms	responsive to L-DOPA	31/17
ND02798 ^a	Heterozygous (duplication exon 6)	56	Tremor predominant; marked dyskinesias; positive FH	responsive to L-DOPA	69/50
ND05921 ^a	Heterozygous (deletion exon 4)	49	Tremor predominant; No dystonia or dyskinesias	responsive to L-DOPA	50/25
ND02639 ^a	Homozygous	30	Akinetic rigid; Marked dyskinesias; s/p bilateral STN DBS	responsive to L-DOPA; sustained response to DBS	57/50
KW	Homozygous	26	Tremor predominant; marked dyskinesias; s/p bilateral Gpi DBS	responsive to L-DOPA; sustained response to DBS	47/21

^a the mutations found in these patients have been described elsewhere[5]; AAO, age at onset; FH, family history.