Published in final edited form as:
Mov Disord. 2009 April 15; 24(5): 662–666. doi:10.1002/mds.22365.

Familial Parkinsonism and early onset Parkinson's disease in a Brazilian Movement Disorders clinic: Phenotypic characterization and frequency of *SNCA, PRKN, PINK1* and *LRRK2* mutations

Sarah Teixeira Camargos, MD[1], **Leonardo Oliveira Dornas, MD**[1], **Parastoo Momeni, PhD**[3], **Andrew Lees, MD, PhD**[4], **John Hardy, PhD**[4,5], **Andrew Singleton, PhD**[2], and **Francisco Cardoso, MD, PhD**[1]

[1]Movement Disorders Group, Neurology Service, Internal Medicine Department, Federal University of Minas Gerais, Minas Gerais, Brazil

[2]Laboratory of Neurogenetics, National Institutes on Aging, National Institutes of Health, MD, USA

[3]Department of Neurology, Texas Tech University Health Sciences Center, TX, USA

[4]Reta Lila Weston Institute of Neurological Studies, University College London, London, UK

[5]Department of Molecular Neuroscience, Institute of Neurology, Queen Square, London, UK

Abstract

The aim of the study was to evaluate the frequency and to perform phenotypic and genotypic characterization of familial Parkinsonism and early onset Parkinson's disease (EOPD) in a Brazilian movement disorder unit. We performed a standardized clinical assessment of patients followed by sequencing of *PRKN*, *PINK1*, *SNCA* and *LRRK2*. During the period of study (January through December, 2006) we examined 575 consecutive patients of whom 226 (39.3%) met the diagnosis of Parkinsonism and idiopathic Parkinson's disease (IPD) was diagnosed in 202 of the latter. Of the IPD cases, 45 (22.3%) had EOPD. The age at onset in the EOPD cases (n=45) was 34.8±5.4 years (mean ±standard deviation). The age at onset in familial the late-onset PD patients (n=8) was 52.3±12.2 years. In the early-onset cases, we identified five known mutations in *PRKN*, two single heterozygous and three compound heterozygous (P153R, T240M, 255Adel, W54R, V3I); in addition we identified one novel mutation in *PINK1* (homozygous deletion of exon 7). In the familial cases (late onset), one patient had a novel *LRRK2* variant, Q923H, but no *SNCA* mutations were identified. We have demonstrated that EOPD accounts for a high frequency of IPD cases in our tertiary referral center. *PRKN* was the most commonly mutated gene but we also identified a novel mutation in *PINK1* and a novel variant in *LRRK2*.

Keywords

LRRK2; *PINK1*; *PRKN*; *SNCA*; Brazil

Introduction

Idiopathic Parkinson's disease (IPD) is the most frequent cause of Parkinsonism, being diagnosed in up to 86% of cases[1]. Early onset PD (EOPD), defined by age of onset between

Corresponding author: Francisco Cardoso cardosofe@terra.com.br, Av Pasteur 89/1107. Belo Horizonte, MG, Brazil Fax 55-31-32134951 Zip code- 30150-290.

20 and 40 years of age[2], accounts for 4-10% of all patients with PD. Recent epidemiologic studies have indicated a more readily evident genetic component in EOPD in contrast to late-onset IPD[3,4]. Several familial forms of PD have been described and mutation in the genes *SNCA, PRKN, PARK7, PINK1, LRRK2* and *GBA* have been associated with genetic forms of PD [5-11]. There is clear evidence that etiologic factors may vary depending on the geographic and ethnic background of the studied population; in particular the prevalence of monogenic forms of PD and specific disease causing mutations can vary considerably between populations[12]. In the current study we describe the frequency of PD, including EOPD and familial forms of PD in cases ascertained within a movement disorders clinic in Brazil; furthermore we examined EOPD and cases reporting a positive family history of parkinsonism for mutations in *SNCA, PRKN, PINK1* and *LRRK2*.

Methods

During the year of 2006 we screened all consecutive patients seen at the Movement Disorders Clinic of the Federal University of Minas Gerais, a tertiary referral center located in the southeast of Brazil, covering an area with a population of 20 million people. All patients with parkinsonism, defined by the presence of bradykinesia and at least one of the following: rigidity, tremor or postural instability, entered the study. IPD was diagnosed according to the UK Brain Bank criteria[13]. Patients were classified as EOPD if the age at onset of parkinsonism was ≤ 40 years and ≥ 20 years[14]. Careful pedigree evaluation and a detailed neurological exam including the application of the UPDRS were performed for each patient[15]. We have calculated the rate of progression of motor disability using the formula: median of UPDRS motor score (when patient is on) within a year minus the basal motor score. Psychiatric problems were diagnosed using DSM- IV criteria[16]. Patients were recruited with their prior written informed consent and ethical committee approval. DNA was extracted from peripheral lymphocytes according to routine procedures. We tested *PRKN, PINK1, SNCA* and *LRRK2* in the late onset PD familial group (n=8) and *PRKN and PINK1* for the EOPD group (n=45). Amplification of the protein coding exons of *PRKN, PINK1, SNCA* and *LRRK2* was performed by polymerase chain reaction in a total volume of 15μl containing 20ng of genomic DNA, 5pmol of forward and reverse primers, 5U of FastStart TaqDNA polymerase (Roche) containing all of the required buffers and dNTPs (details available upon request). Thermal cycling was performed using a standard 60-50 touchdown PCR program. Following confirmation of amplification on a 2% agarose gel, PCR products were purified by filtration on 96 well plates (Millipore). The product was then used as template in a dye-terminator sequencing reaction performed as per the manufacturer's protocol (BigDye® Terminator v3.1, Applied Biosystems, Foster City, CA). Each product was sequenced in both forward and reverse directions with the primers used for initial amplification. The resulting products were filter purified as above and run on an ABI3730XL; all data was analyzed using Sequencher (GeneCodes Corporation). To assay for genetic dosage alterations, quantitative duplex PCR of genomic DNA samples was performed on the ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Protein coding exons of *PRKN, PINK1* and exon 7 of *SNCA* were each co-amplified with βglobin, which served as an endogenous standard. PCR was carried out with TaqMan Universal PCR Master Mix using 25 ng genomic DNA, 900 nmol/L primers, and 250 nmol/L probes in a total reaction volume of 20 μL (Applied Biosystems). Primers and probes as well as PCR conditions are as previously published[17,18]. The cycle in the log phase of PCR amplification at which a significant fluorescence threshold was reached (Ct) was used to quantify each amplimer. The dosage of each amplimer relative to the reference gene and normalized to control DNA was determined using the $2^{-\Delta\Delta Ct}$ method. To be considered valid, the requirements were SDs < 0.16 and threshold values reached before cycle 28. A value was considered a heterozygous deletion between 0.4 and 0.6, normal between 0.8 and 1.2, a heterozygous duplication between 1.3 and 1.7, and a triplication or homozygous duplication between 1.8 and 2.2.

Results

During the year of 2006 we examined 575 patients, of whom 226 met the diagnosis of Parkinsonism. IPD was diagnosed in 202 with 45 EOPD cases. Eight late onset familial cases were included in this study. Age at onset of the EOPD group was 34.8 ± 5.4 years (mean ± standard deviation); eight reported a positive family history for IPD, of whom seven showed a pattern of inheritance consistent with autosomal recessive transmission; the remaining patient reported a family history suggestive of an autosomal dominant mode of inheritance. The age at onset of the late onset PD group was 52.3±12.2 years; four had a pattern of inheritance consistent with autosomal recessive transmission and four patients reported a family history suggestive of autosomal dominant disease.

For the early onset cases, we identified 13.3% of patients with mutations: five previously reported mutations in *PRKN:* P253R in a compound heterozygosity with exon 5 duplication; T240M in a single heterozygosity and in compound heterozygosity with 255Adel; 255Adel in a single heterozygosity; W54R in a compound heterozygosity with V3I and one novel mutation in *PINK1*, a homozygous deletion of exon 7 (Fig 1). Clinical data of these patients are found in Tables 1 and 2. For the familial late onset cases, only one patient (5.5%) had a coding alteration absent from controls in the screened genes: a novel *LRRK2* variant (Q923H) (Fig 2).

Discussion

In a previous study at our clinic, IPD was identified in 70% of 338 patients followed up from 1993 to 1995. During 2006, we have diagnosed 89.5% of all 226 consecutive patients with Parkinsonism. In our series, 22.3% of all IPD cases met criteria for EOPD. This is certainly more than expected for the general population, but, as is well recognized, in a tertiary center atypical patients are often over represented[19]. Nevertheless, this EOPD frequency is not very different than what was found in a community-based study, where it accounted for 17% of all parkinsonian patients[20]. Bower and colleagues found an incidence of EOPD of 0·8 cases per 100,000 per year in those aged 0–29 years, rising to 3·0 per 100,000 per year in those aged 30–49 years[21]. In a Korean series of EOPD, 5% of 94 patients had *PRKN* mutations (all in compound heterozygous state) and none had *PINK1* mutations[22]. The frequency of those mutations within an Italian early onset group of patients was 8% (5% simple heterozygous mutations, 1% compound heterozygous and 1% homozygous)[23]. In a recent study, Clark et al, showed a *PRKN* mutation prevalence of 12.9% among 101 early onset cases; 10.9% carried simple heterozygous mutations, 1% homozygous and 1% compound heterozygous mutations[24]. The range of mutations in sporadic cases in previous studies varied between 9 and 18% with single mutations counting with 6.1 up to 12.8%[25-27]. According to Klein et al., mutation of *PRKN* occurs in 20% of European early onset cases, while *PINK1* mutations occur in 2% to 7%[23]. Our data are also in agreement with such studies (*PRKN*, 11.1% and *PINK1*, 2.2% of cases) in EOPD. Single heterozygous mutations accounted with 4.4% in *PRKN* and 6.6% were compound heterozygous mutations. One patient hat a homozygous mutation in *PINK1*. Our findings suggest that despite the genetic heterogeneity of the contemporary Brazilian population, a result of mixture of people of European (mostly Portuguese but also Italian, German and other nationalities), African and Native origins, the frequency of these genetic mutations does not differ substantially from populations from other geographic areas. Surprisingly, since mutations in *PRKN* are highly correlated with lower age of onset and positive family history[23], none of the familial early onset cases had mutation of the screened genes. One possible explanation for this finding is the small sample size. The clinical picture of patients with and without mutations was similar in the studied population. Two patients carrying single heterozygous mutations of *PRKN* did not differ from the three compound heterozygous subjects or from those patients without mutations. Whether these single heterozygous mutations play a role in the disease process remains to be determined. Two

previous studies showed that single heterozygous mutations in *PRKN* are as common as in controls[28,29]. This was not confirmed in a third sudy[30]. Some individuals carrying a heterozygous mutation in *PRKN* or *PINK1*, considered as "asymptomatic patients" had some minor but unequivocal parkinsonian features[31-33]. PET scan studies of *PRKN* heterozygous mutant carriers showed reduction of striatal F-Dopa uptake[34]. Haploinsufficiency, a dominant negative effect or a risk factor associated to an environmental or another genetic cause have been used as hypotheses supporting the role of a single recessive mutation in promoting parkinsonism in these patients[33,35,36]. Since the frequency of *PRKN* mutations is higher in the EOPD group, it is possible that mutations in this gene might diminish the age at onset.

We did not find mutations or gene dosage alterations in *SNCA*. This confirms the findings of several other authors that *SNCA* mutation is a rare cause of parkinsonism, regardless of the age of onset of the patients[37,38]. *LRRK2* mutations are more common, one study with 504 PD cases (of whom were 245 EOPD cases) and 341 controls showed a *LRRK2* mutation frequency of ~1% in sporadic cases and ~5% in familial cases[39]; although as these studies primarily screen a single exon/mutation, they are likely an underestimation of the true prevalence. We tested all exons of *LRRK2* only in familial cases (n=8) and we identified variant Q923H located in exon 21 in a typical PD case with a clear autosomal dominant inheritance. The new variant was not found in 192 healthy controls. Cross species comparison reveals a reasonable conservation of this residue. Although these findings support a pathogenic effect of this novel mutation, this result must be interpreted with caution. We were not able to study disease segregation in this family since the patients parents were deceased and thus we feel it remains to be determined if this variant is pathogenic. We did not identify the common G2019S mutation in our series, although given the relatively small sample series this is perhaps not surprising.

Prevalence studies of known genes in a larger number of patients are needed to provide a better view about the role of these mutations in the Brazilian population, whether it influences clinical features and age at onset.

Acknowledgments

We thank the patients for taking part in this study. This work was supported in part by the Intramural Research Program of the National Institute on Aging, National Institutes of Health, Department of Health and Human Services. The NIH project number associated with this work is Z01 AG000957-05.

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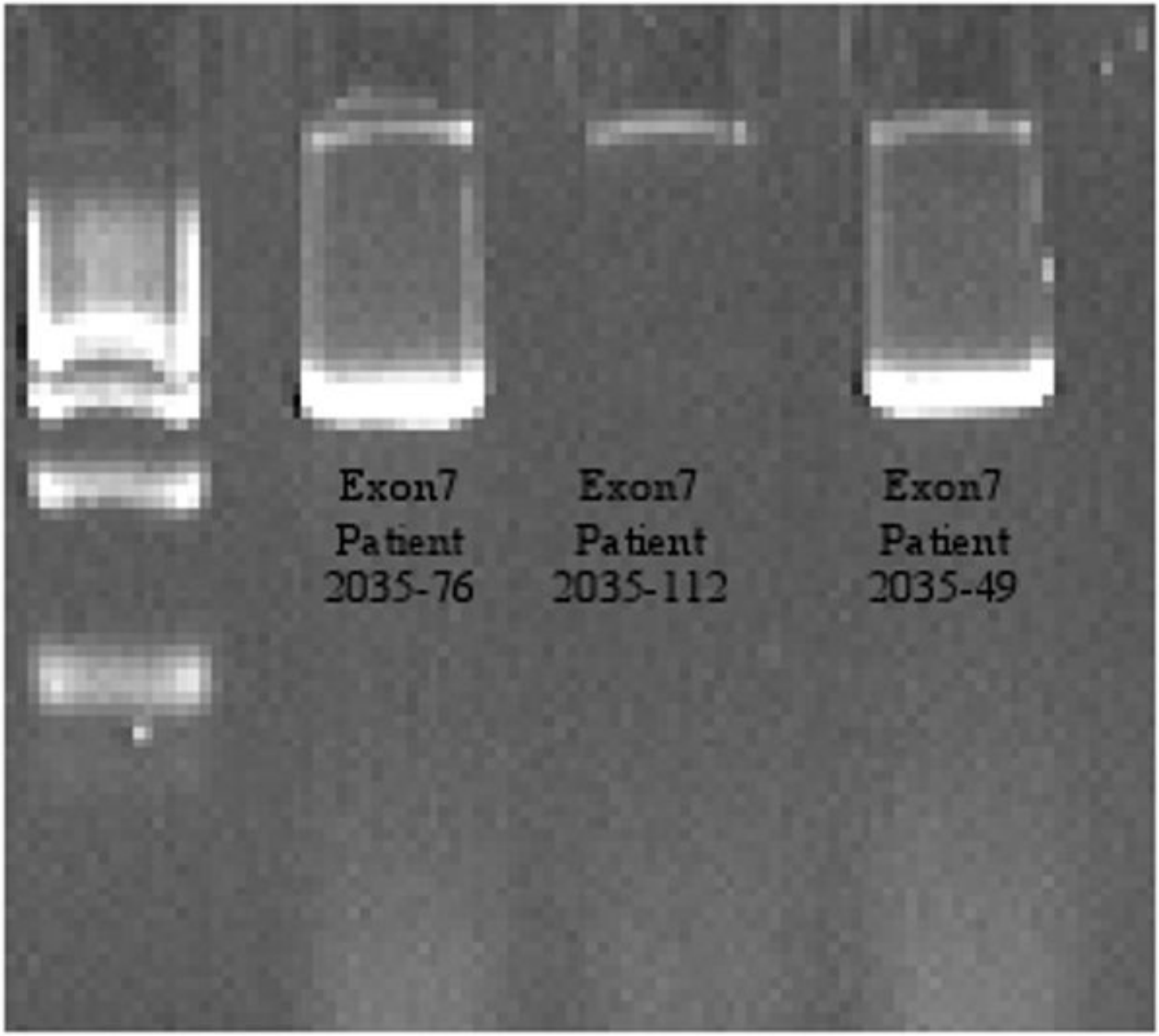

Figure 1.
Confirmation of amplification on a 2% agarose gel. *PINK1* exon 7 homozygous deletion (patient 2035-112)

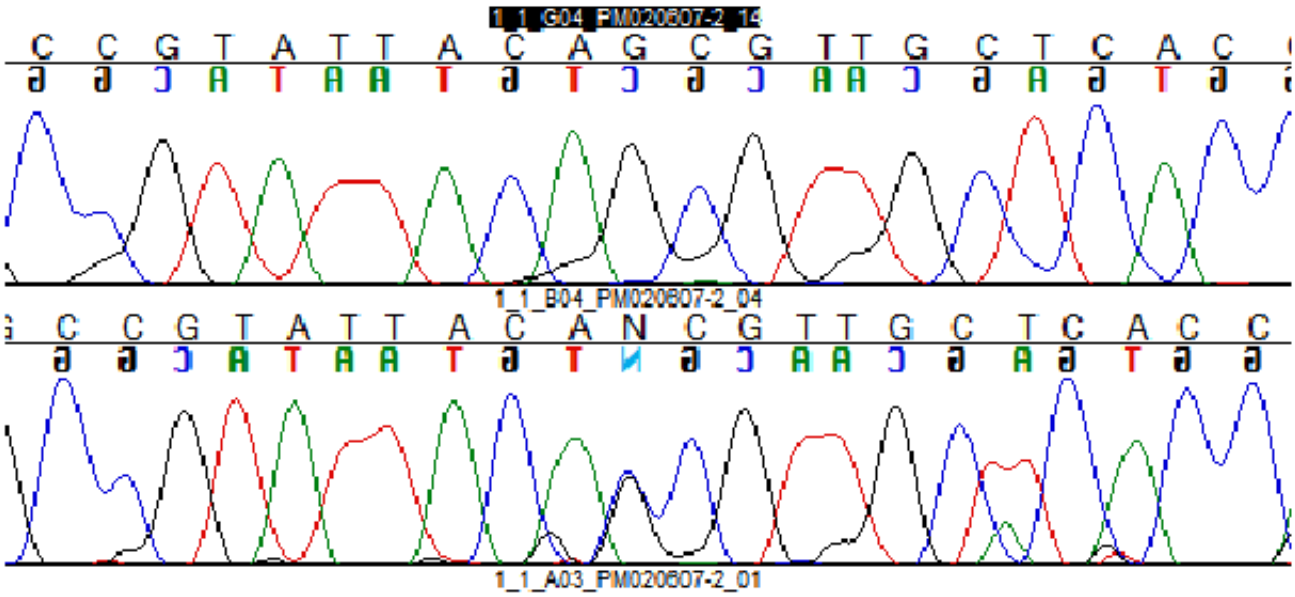

Figure 2.
Novel mutation in *LRRK2* - Q923

Table 1

Clinical Features of Patients with Mutations

Patient	**2035-21**	**2035-23**	**2035-46**	**2035-49**	**2035-76**	**2035-112**	**2035-43**
Gene	*PRKN*	*PRKN*	*PRKN*	*PRKN*	*PRKN*	*PINK1*	*LRRK2*
Mutation	W54R	255Adel	T240M	P253R	255Adel	Ex7 del	Q923H
	V3I			Dup exon5	T240M	Ex7 del	
Gender	Male	Female	Male	Male	Male	Female	Female
Current Age	54	52	38	46	64	43	51
Age et Onset	40	40	33	40	22	24	46
First symptom	Bradikynesia	Lower limb tremor	Tremor	Bradikynesia	Tremor	Tremor	Tremor
Follow up (years)	7	7	2	4	11	14	2
Family History	Negative	Negative	negative	negative	negative	negative	Positive (father and one brother)
UPDRS –III (On)	50	12	17	54	36	10	52
Progression rate (on motor score/ year)	+2.5/year	+0.3/year	+1/year	+4/year	+0.8/year	+0.5/year	+5/year
Type	Rigid-akinetic	Tremor-dominant	Tremor-dominant	Rigid-akinetic	Tremor-dominant	Tremor-dominant	Rigid-akinetic
Neuroimaging	Normal CT scan	Normal MRI	Normal MRI	Normal CT scan	Normal CT scan	Normal MRI	Normal MRI
Time for ldopa use (from the first symptom)	5 years	*	*	1 year	15 years	6 years	4 years
Time to develop dyskinesias	2 years	------	-------	4 years	1 year	7 years	--------
Dyskinesias – (UPDRS score)	1-1-2-0	0	0	1-0-0-0	1-2-2-1	1-0-0-0	0
Surgery	No	No	No	No	Palidotomy	No	No
Psychiatric Symptoms	None	Generalized Anxiety Disorder	Depression	Anxiety	None	Anxiety	Depression

*Patients not treated with Ldopa

Table 2

Clinical Comparison Between EOPD With and Without mutations

	With mutation	Without mutation
N	6	39
Age at onset	33.1±7.6	35±5.4
Male × female	4 × 2	20 × 19
Familiar history	all negative	8
Response to ldopa		
Haven't been using	15.4 %	33.3%
Good response	76.9 %	66.6%
Intolerance	7.7 %	----
Type		
Rigid-akinetic	59%	33.3%
Tremor dominant	41%	66.6%
Dyskinesias	66.6%	76.9%