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ORIGINAL PAPER

Influence of *DRD1* and *DRD3* Polymorphisms in the Occurrence of Motor Effects in Patients with Sporadic Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a multisystem disorder that affects 2–3% of the population ≥ 65 years of age. The main pharmacologic agent use in the treatment of clinical symptoms of PD is levodopa (L-DOPA). However, the chronic use of L-DOPA might result in the emergence of motor complications such as motor fluctuation and dyskinesia. Previous studies have shown that the inter-individual variability and pharmacogenetic profile of PD patients seem to influence the occurrence of motor complications. For these reasons, the purpose of this study was to evaluate a possible relationship between *DRD1* A48G and *DRD3* Ser9Gly genetic variants with the occurrence of motor complications in PD patients in a Brazilian population. A total of 228 patients with idiopathic PD were enrolled. Patients were genotyped for *DRD1* A48G and *DRD3* Ser9Gly polymorphisms using PCR–RFLP. The univariate and multivariate analyses were performed to assess the association of these polymorphisms with the occurrence of motor fluctuation and dyskinesia in PD patients. Multiple Poisson regression analyses showed a protector effect to the occurrence of dyskinesia for individuals carrying of the *DRD1* G/G genotype (PR 0.294; CI 0.09–0.87; $p \leq 0.020$) after the threshold Bonferroni's. Besides, we verified risk increased to the occurrence of motor complications with daily L-DOPA dosage, disease duration, and users of rasagiline, selegiline, or entacapone ($p < 0.05$ for all). Our results suggest that the DRD1 A48G polymorphism and the presence of extrinsic and intrinsic factors may role an effect in the occurrence of dyskinesia in PD patients.

Keywords Dyskinesia · Pharmacogenetic · Parkinson disease (PD) · Genetic variation · Dopamine receptors (DR)

Introduction

Parkinson's disease (PD) is a multisystem disorder characterized by progressive dopaminergic cell degeneration in the substantia nigra pars compacta (SNc) (Cuenca et al. 2018; DeMaagd and Philip 2015; Olanow et al. 2009). The clinical manifestations of PD include both motor and non-motor symptoms that are associated with reduced health-related quality of life of the PD patients (Kalia and Lang 2015; Poewe et al. 2017). This disorder affects 2–3% of the population ≥ 65 years of age and up to 2030, it is expected that around 8.7 million individuals will suffer from PD. Regarding the Brazilian population, it was estimated the prevalence of 443/100,000 for the individuals ≥ 60 years and a projection of 0.34 million for 2030 (Dorsey et al. 2007). In relation to other neurodegenerative disorders such as dementia, it was estimated the standardized prevalence of 7.07 in the Latin America population

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(Fagundes et al. 2011; Nitrini et al. 2009). The etiology of PD is considered to be complex involving genetic and environmental factors (Kalia and Lang 2015; Poewe et al. 2017; Sauerbier et al. 2018; Surmeier et al. 2017).

The major pharmacological agent used to treat symptoms of PD is Levodopa (L-DOPA) (Schumacher-Schuh et al. 2014a, b). L-DOPA is a dopamine precursor considered the "gold standard" and the most potent medication to improve the clinical aspects of this disorder (Tran et al. 2018). Despite L-DOPA improved symptoms of Parkinsonism, with a dose-related response, after a period of chronic use it was found to be associated with appearing adverse outcomes such as motor fluctuations and dyskinesia in PD patients (Freitas et al. 2017; Kalia and Lang 2015; Schumacher-Schuh et al. 2014a, b; Tran et al. 2018). The phenomenon of motor fluctuations consists of alterations between periods of good motor symptom control (i.e., on-time) and periods of reduced motor symptom control (i.e., off-time). Dyskinesia is characterized by hyperkinetic involuntary movements which occur most frequently when L-DOPA concentrations are at their maximum in the plasma (Freitas et al. 2017; Kalia and Lang 2015; You et al. 2018). These motor complications affect 40% of PD patients after 4–6 years of treatment (Ahlskog and Muenter 2001; Nutt 2001).

Many factors help to predict the occurrence of motor complications in the course of PD. The most important risk factors include disease progression, disease severity, higher individual doses of L-DOPA, clinical subtype, body weight, peripheral pharmacokinetic factors affecting absorption of L-DOPA and possibly genetic risk factors (Comi et al. 2017; Freitas et al. 2017; Sharma et al. 2010). However, the pathophysiology of occurrence of motor complications is quite complex and not fully understood (Tran et al. 2018).

Previous studies have to evidence the contribution of dopamine as a major player in the development of motor complications (Calabresi et al. 2008; Fabbrini et al. 2007). In addition, reports suggest that genetic predisposition can be determinant in the occurrence of these motor side effects in PD patients (Comi et al. 2017; Kusters et al. 2018), once that, exist a profound inter-individual heterogeneity between these patients (Thanvi et al. 2007; You et al. 2018).

Genetic variants in the dopamine receptors (DR) genes are natural candidates for being researched in the occurrence of motor complications such as dyskinesia and motor fluctuations. Once that, these genes form basal ganglia circuitry pathways and they are associated with movement control (Drozdzik et al. 2014; Kalinderi et al. 2011). D1 and D3 are DR encoded by *DRD1* and *DRD3* genes, respectively. Variations in these genes can alter the levels of expression of these receptors and this way, change of absorption and intracellular signaling of dopamine. This process may favorite in the occurrence of motor complications such as dyskinesia in PD patients (Missale et al. 1998; Schumacher-Schuh et al. 2014a, b; Tran et al. 2018; You et al. 2018).

Despite this relevancy, few studies have been performed to evaluate the role of genetic variations in the *DRD1* and *DRD3* genes with the occurrence of motor complications in PD. Regarding the *DRD1* gene, to the best knowledge, only two studies evaluated the association of the *DRD1* A48G polymorphism with the occurrence of dyskinesia in PD patients and did not find association between the investigated variables. (Comi et al. 2017; Oliveri et al. 1999). Regarding *DRD3* gene an association between *DRD3* Ser-9Gly polymorphism and the occurrence of dyskinesia was observed, but this result was not confirmed by other studies (Comi et al. 2017; Kaiser et al. 2003; Lee et al. 2011; Paus et al. 2009).

To clarify the effect of these genetic variants on the occurrence of adverse outcomes such as dyskinesia and motor fluctuation in the treatment of PD, the present study aimed to investigate a possible association of the *DRD1* A48G and *DRD3* Ser9Gly polymorphisms with the occurrence of motor fluctuations and dyskinesia in PD patients.

Patients and Methods

Patients

A total of 228 consecutive patients were enrolled in this cross-sectional study. The patients were attended at the PRO-PARKINSON service from the Clinics Hospital of Pernambuco, between January 2016 and December 2017. The diagnosis of idiopathic PD was based on the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hoehn and Yahr 1967) and revised by an experienced neurologist. In addition, PD patients undergoing L-DOPA treatment in monotherapy or combined with other antiparkinsonian drugs were enrolled for at least 1 year. Study patients who presented atypical manifestations or secondary parkinsonism were excluded . The study protocol was approved by the local independent ethics committee of The Ministry of Health (Brazil) (CAAE: 45614415.0.0000.5208). All participants provided written, informed consent of participation before the initiation of any study procedures. Relevant clinical and demographic features of the study population such as gender, age, age at onset, disease duration, daily dosage of levodopa, duration of levodopa therapy, presence of dyskinesia, motor fluctuations and severity of the disease based on the Hoehen-Yahr (HY) (Hoehn and Yahr 1967) score were obtained through medical records and in a face-to-face interview with the patients and their family members.

Motor fluctuations were determined based on a score of one or more on question 39 of the Unified Parkinson's Disease Rating Scale (UPDRS) part 4 and/or ingestion of

levodopa five or more times a day (dos Santos et al. 2018; Schumacher-Schuh et al. 2014a, b). The presence of dyskinesia was defined as drug-induced hyperkinetic or dystonic movements or postures or both (Hagell and Widner 1999) and/or if patients had a score of one or more on question 32 of the UPDRS part 4 and/or if patients were in use of amantadine as an antidyskinetic drug (Martínez-Martín et al. 1994; Rieck et al. 2012).

DNA Extraction and Genotyping

Genomic DNA was extracted from 3 mL of the venous peripheral blood of PD individuals using a Wizard Genomic DNA Purification Kit (Promega, Madison, Wisconsin) and stored in a −20 °C freezer. This procedure was performed at the GENOMA at the Federal Rural University of Pernambuco. Genotyping for *DRD1* (rs4532) and *DRD3* (rs6280) were performed as described by Comi et al. and Damasceno dos Santos et al. (Comi et al. 2017; Damasceno dos Santos et al. 2019).

Statistical Analyses

The genotype distribution and allele frequencies of the polymorphisms were obtained by direct counting. The Hardy–Weinberg equilibrium (HWE) test was applied to datasets using the Bioestat 5.0 program. Univariate and multivariate statistical analyses were performed using the R software, version 3.0.2 (http://www.R-project.org/). The association for categorical variables was verified with the Chi square test. The Student's *t* test was realized for continuous data with normal distribution and the Wilcoxon–Mann–Whitney test was performed for data without a normal distribution. The Kolmogorov–Smirnov test was used to evaluate normality. Genotype frequencies were analyzed by the Chi square test (χ^2) and the odds ratio (OR) with 95% confidence interval (CI) was calculated using the tool for single-nucleotide polymorphism (SNP) analysis SNPStats (https://www.snpstats.net/start.htm). Data are shown as the mean ± standard deviation (SD) and as median with 25th–75th percentiles, as appropriate.

Multivariate analyses was performed by multiple Poisson regression with robust standard errors used to assess the effect of polymorphisms on the occurrence of motor fluctuations and dyskinesia, since the outcome was a frequent event in our sample (Greenland 2004), while potential confounders to be entered in models were defined based on conceptual analyses of the literature and/or by means of a statistical definition. A formal Bonferroni correction for the number of analyzed SNPs would require a significance threshold of $p = 0.025$. The post hoc statistical power analysis was performed with the G*power software (version 3.1.5) performed 92% power for analysis.

Results

Clinical and demographic variables for all PD patients enrolled in this study are presented in Table 1. Motor fluctuation and dyskinesia were assessed only as a categorical variable (presence/absence) and were present in 44.3% and 22.8% of the patients, respectively. We verified significant

Table 1 Clinical and demographic characteristics of PD patients: all and stratified by the occurrence of motor fluctuation and dyskinesia

	All	Motor fluctuation		*p* (value)	Dyskinesia		*p* (value)
		No	Yes		No	Yes	
Patients (%)	228	101 (44.3)	127 (55.7)		176 (77.2)	52 (22.8)	
Men (%)	131 (57.4)	54 (41.2)	77 (58.8)	0.2771	101 (77.1)	30 (22.9)	0.9687
Age at onset years, median	65 (57–72)	66 (59–74)	63 (55–70)	**0.0276***	58 (50–64)	51 (44–60)	**0.0006***
Disease duration, years, median	7 (5–10)	5 (3–8)	8 (5–11)	**< 0.0001***	6 (4–9)	9 (7–12)	**< 0.0001***
Levodopa therapy duration years, mean ± S.D.	6.71 ± 3.99	5.64 ± 3.87	7.56 ± 3.89	**< 0.0001**	6.28 ± 3.99	8.17 ± 3.66	**0.0002***
Levodopa dosage, mean ± S.D.	705.59 ± 329.62	560.14 ± 224.42	821.25 ± 354.03	**< 0.0001**	655.67 ± 296.37	871.15 ± 382.11	**< 0.0001***
Dopamine agonist use (%)	145 (63.6)	64 (44.2)	81 (55.8)	0.9894	103 (71)	42 (29)	**0.0034**
COMT inhibitor use (%)	55 (24.1)	2 (3.6)	53 (96.4)	**< 0.0001**	34 (61.8)	21 (38.2)	**0.0018**
MAOB inhibitor use (%)	58 (25.4)	3 (5.2)	55 (94.8)	**< 0.0001**	42 (72.4)	16 (27.6)	0.8667
HY stage, median	2 (2–3)	2 (2–2)	2 (2–3)	**0.0007***	2 (2–3)	3 (2–3)	**0.0013**

The median (first quartile–third quartile) values for data without a normal distribution. *p* (values) calculated by *t* test or by *Wilcoxon–Mann–Whitney U-test (quantitative variables with or without normal distribution, respectively), and chi-square test (categorical variables)

COMT catechol-O-methyl transferase, *MAOB* Monoamine oxidase inhibitor, ± *s.d.* standard derivation, *HY* Hoehn and Yahr scale

differences among the occurrence of motor fluctuations with younger age at onset of motor symptoms ($p=0.0276$), longer disease duration ($p<0.0001$), major time of L-DOPA therapy ($p<0.0001$), high doses daily of L-DOPA ($p<0.0001$) and severity of the disease based on Hoehn–Yahr score ($p=0.0007$). Additionally, there were significant associations for combined therapy with catechol-o-methyl transferase (COMT) and monoamine oxidase (MAOB) inhibitors ($p<0.0001$ for both). Regarding the occurrence of dyskinesia also there were significant differences with these features mentioned above ($p<0.005$ for all). Additionally, we observed an association between dopamine agonist use with the occurrence of dyskinesia ($p=0.0034$) (Table 1).

All genes investigated were in HWE (data not shown). The genotype distribution, allele frequencies and univariate analyses for evaluating the effect of the *DRD1* (rs4532) and *DRD3* (rs6280) genetic variants in the occurrence of motor fluctuations and dyskinesia are shown in Table 2. No associations were observed among *DRD1* and *DRD3* genes polymorphisms and the occurrence of motor fluctuation as well as dyskinesia ($p>0.05$).

Multiple Poisson regression analyses were used to perform a possible relation between the *DRD1* (rs4532) and *DRD3* (rs6280) polymorphisms with the occurrence of motor complications such as motor fluctuation and dyskinesia, controlling for the conceptual confounders previously described. We verified that occurrence of motor fluctuation was associated with daily L-DOPA dosage (prevalence ratio (PR) 1.000; CI 1.00–1.01; $p=0.010$), use of rasagiline (PR 2.110; CI 1.74–2.54; $p<0.0001$), use of selegiline (PR 1.838; CI 1.40–2.40; $p<0.0001$) and use of entacapone (PR 1.902; CI 1.55–2.33; $p<0.0001$) (Table 3). Among the clinical features investigated for occurrence of dyskinesia we observed association with disease duration (PR 1.217; CI 1.03–1.42; $p=0.016$), daily L-DOPA dosage (PR 1.000; CI 1.00–1.03; $p=0.043$) and use of alcohol (PR 2.015; CI 1.16–3.47; $p=0.012$) (Table 4).

Regarding polymorphisms investigated, an association between *DRD1* (rs4532) and the occurrence of dyskinesia were verified after the threshold Bonferroni's correction. Individuals carrying *DRD1* G/G genotype presented prevalence ratio for a protector effect in the occurrence of dyskinesia (PR 0.294; CI 0.09–0.87; $p\leq0.020$). In contrast, the analysis of rs6280 in the *DRD3* gene presented no statistical association with the occurrence of motor fluctuation as well as dyskinesia (Tables 3 and 4).

Discussion

The long-term outlook for the PD patient is impaired because of the appearance of motor complications such as motor fluctuations and dyskinesia. These phenomena

Table 2 Univariate analyses of the relation of the rs4532, rs6280 on the occurrence of motor fluctuation and dyskinesia

	All	Motor fluctuation		X^2 (p*)	OR (CI 95%)	p*	Dyskinesia		X^2 (p*)	OR (CI 95%)	p*
rs4532	228	No (101)	Yes (127)				No (176)	Yes (52)			
A/A (%)	119 (52.2)	50 (49.5)	69 (54.3)	1.322 (0.516)	1.00		86 (48.9)	33 (63.5)	3.574 (0.167)	1.00	
A/G (%)	88 (39)	43 (42.6)	45 (35.4)		0.76 (0.44–1.32)	0.52	72 (40.9)	16 (30.8)		0.58 (0.30–1.14)	0.16
G/G (%)	21 (8.8)	8 (7.9)	13 (10.2)		1.17 (0.45–3.05)	0.92	18 (10.2)	3 (5.8)		0.43 (0.12–1.57)	0.30
AA (%)	119 (52.2)	50 (49.5)	69 (54.3)	0.525 (0.468)	1.00		86 (48.9)	33 (63.5)	3.428 (0.064)		
AG+GG (%)	109 (47.8)	51 (50.5)	58 (45.7)		0.82 (0.49–1.39)	0.47	90 (51.1)	19 (36.5)		0.55 (0.29–1.04)	0.09
rs6280											
Gly/Gly	43 (18.8)	18 (17.8)	25 (19.7)	1.210 (0.546)	1.00		31 (17.6)	12 (23.1)	1.881 (0.390)	1.00	
Ser/Gly	162 (71.1)	75 (74.3)	87 (68.5)		0.84 (0.42–1.65)	0.54	125 (71)	37 (72.2)		0.76 (0.36–1.64)	0.36
Ser/Ser	23 (10.1)	8 (7.9)	15 (11.8)		1.35 (0.47–3.86)	0.76	20 (11.4)	3 (5.8)		0.39 (0.10–1.55)	0.28
Gly/Gly	43 (18.8)	18 (17.8)	25 (19.7)	0.939 (0.454)	1.00		31 (17.6)	12 (23.1)	0.783 (0.376)		
Ser/Gly+Ser/Ser	185 (81.2)	83 (82.2)	102 (80.3)		0.88 (0.45–1.73)	0.85	145 (82.4)	40 (76.9)		0.71 (0.34–1.51)	0.38

p* p values, X^2 Chi- square

Table 3 Multiple Poisson regression model adjusted for clinical variables, *DRD1* (rs4532) and *DRD3* (rs6280) polymorphisms predicting the occurrence of motor fluctuation in Parkinson's disease patients

	Prevalence ratio	95% CI	*p*-value
Interception	0.208	0.91–0.47	< 0.001
Age	0.995	0.98–1.00	0.368
Disease duration	1.042	0.95–1.13	0.356
Gender (male)	1.140	0.92–1.41	0.232
Levodopa therapy duration	0.988	0.90–1.07	0.778
HY	1.054	0.92–1.19	0.420
Levodopa dose	1.000	1.00–1.01	**0.010**
Alcohol use	1.041	0.74–1.44	0.813
Cigarettes use	1.038	0.73–1.47	0.834
Dopaminergic agonist			
Pramipexole use	0.966	0.78–1.19	0.750
Rotigotine use	0.837	0.47–1.49	0.547
MAOBIs			
Selegiline use	1.838	1.40–2.40	**< 0.001**
Rasagiline use	2.110	1.74–2.54	**< 0.001**
COMTIs			
Entacapone use	1.902	1.55–2.33	**< 0.001**
rs6280			
Ser/Ser	1.194	0.83–1.71	0.338
Ser/Gly	1.003	0.78–1.28	0.984
rs4532			
G/G	0.968	0.68–1.36	0.852
G/A	0.978	0.78–1.22	0.844

Significant *p* values are shown in bold

COMTIs, catechol-O-methyltransferase inhibitors; MAOBIs, monoamine oxidase type B inhibitors

Table 4 Multiple Poisson regression model adjusted for clinical variables, *DRD1* (rs4532) and *DRD3* (rs6280) polymorphisms predicting the occurrence of dyskinesia in Parkinson's disease patients

	Prevalence ratio	95% CI	*p*-value
Interception	0.125	0.01–0.87	0.036
Age	0.976	0.94–1.00	0.100
Disease duration	1.217	1.03–1.42	**0.016**
Gender (male)	0.903	0.57–1.40	0.654
Levodopa therapy duration	0.878	0.74–1.03	0.117
HY	1.238	0.90–1.69	0.180
Levodopa dose	1.000	1.00–1.03	**0.043**
Alcohol use	2.015	1.16–3.47	**0.012**
Cigarettes use	1.047	0.58–1.88	0.787
Dopaminergic agonist			
Pramipexole use	1.442	0.78–2.66	0.243
Rotigotine use	1.879	0.75–4.76	0.172
MAOBIs			
Selegiline use	1.324	0.52–3.30	0.551
Rasagiline use	1.354	0.80–2.26	0.248
COMTIs			
Entacapone use	1.373	0.82–2.29	0.227
rs6280			
Ser/Ser	0.656	0.19–2.19	0.494
Ser/Gly	1.116	0.63–1.96	0.703
rs4532			
G/G	0.294	0.09–0.87	**0.020**
G/A	0.756	0.44–1.29	0.311

Significant *p* values are shown in bold

COMTIs catechol-O-methyltransferase inhibitors, *MAOBIs* monoamine oxidase type B inhibitors

are characterized by modification of molecular basis in pre and postsynaptic neurons (Tran et al. 2018; You et al. 2018). Previous studies have suggested that polymorphisms in genes related to dopamine uptake pathway such as DR could be involved in the occurrence of these motor complications (Comi et al. 2017; Drozdzik et al. 2014; Kaiser et al. 2003; Schumacher-Schuh et al. 2014a, b). In addition, side effects such as dyskinesia and motor fluctuations may severely impair the daily life of PD patients (Balestrino and Martinez-Martin 2017; Gilgun-Sherki et al. 2004). For these reasons, the identification of new biomarkers predicting the occurrence of motor complications is a priority in the PD clinical context. We investigated a possible association of the *DRD1* A48G and *DRD3* Ser9Gly polymorphisms with the occurrence of motor fluctuation and dyskinesia in PD patients treated with dopamine replacement therapy in a Brazilian population.

Motor fluctuation is a phenomenon characterized by wearing-off, i.e. worsening or reappearance of motor symptoms in the interval of L-DOPA doses resulting in an 'off' state (Marsden and Parkes 1976). Motor complications affect virtually all patients. However, the rate of it is occurrence is highly variable, affecting ~ 10% of patients per year (Marsden and Parkes 1976). Ahlskog and Muenter (2001) showed that motor fluctuation was present in approximately 40% of patients by 4–6 years of treatment. Our results showed a rate of 55.7% of motor fluctuation in PD patients with 8 (5–11) years of treatment (Ahlskog and Muenter 2001). This superior finding could be explained considering the difference of time of occurrence of motor fluctuations between studies. Dyskinesia is hyperkinetic involuntary movements triggered by high concentration of L-DOPA in the plasma (Marsden and Parkes 1976). The incidence of dyskinesia in PD patients was estimated to vary from 30 to 80% (Jenner 2008). Our outcomes showed a rate of 22.8% of dyskinesia even after 9 (7–12) years of treatment. This discrepant data could be explained considering that dyskinesia was assessed only as a categorical variable (presence/absence).

Besides, we verified association between the occurrence of motor complications with younger age at onset of motor symptoms, longer disease duration, major time of L-DOPA therapy, high doses daily of L-DOPA, higher severity of

the disease (based on Hoehn-Yahr score) and use COMT inhibitors ($p < 0.05$ for all). These findings corroborate the results reported by Tran et al. (2018), Freitas et al. (2017) and Sharma et al. (2010) that highlights the combination of extrinsic and intrinsic factors in the development of motor fluctuations and dyskinesia in PD patients.

Regarding the *DRD3* Ser9Gly polymorphism, no significant difference was verified between the occurrence of motor fluctuation or dyskinesia in both univariate and multivariate analyses. These findings corroborating with the studies of Kaiser et al. (2003), Paus et al. (2009) and Comi et al. (2017). Lee et al. (2011) when extracted their patients into diphasic and peak-dose dyskinesia in PD, it was observed an association between the presence of *DRD3* Ser9Gly polymorphism and the occurrence of diphasic dyskinesia. This distinct finding can be explained by the fact that in our study did not extract PD patients into diphasic and peak-dose dyskinesia. Moreover, the different analysis could result in the discrepancy between the studies. Once, our results were performed through multiple Poisson regression.

In this study, we observed a protector effect in the occurrence of dyskinesia in carriers of *DRD1* G/G genotype after Bonferroni's correction (PR 0.294; CI 0.09–0.87; $p \leq 0.020$). The mechanism of action in which genetic variations in DR genes may favor or protect the occurrence of motor complications in PD patients is not fully understood and is open to discussion. There are some explanations related to genetic variants responsible for modulation of D1 gene. First, *DRD1* A48G polymorphism may impact in the D1 expression (Huang et al. 2008); Second, selective inhibition of the D1 resulted in an increase of metabolized dopamine in the striatum of Rat (Bueno-Nava et al. 2012); Third, studies related that variants in the *DRD1* gene may modulate the response to exogenous L-DOPA and the neuroplasticity neuronal (Carta et al. 2017; Forero et al. 2015). Thus, we can suggest that as dyskinesia is a clinical phenomenon conceptually linked to hyperdopaminergic states, the *DRD1* A48G polymorphism might act as a protective in the occurrence of dyskinesia, once this polymorphism may affect the *DRD1* expression level (Huang et al. 2008).

Following this line of reasoning, our study was the pioneer to show an association between *DRD1* A48G (rs4532) and the occurrence of dyskinesia. Once, previous findings failed to find association between *DRD1* A48G polymorphism and the occurrence of dyskinesia (Comi et al. 2017; Oliveri et al. 1999). A possible explanation for these discrepant finding could be explained due to true effect is not consistently detected due to the low power of previous studies. Furthermore, our study was conducted in a different population (genetic heterogeneity), associated with several other cofactors such as clinical characteristics including the genetic profile.

We are aware that the overall findings presented in our study have some limitations that need to be carefully considered: (1) Although our sample size has power to find the differences observed, the sample size was moderate and additional studies with larger samples are needed to confirm the present findings; (2) This study is cross-sectional and it was not possible to trace the exact time that each patient takes to development of the motor complications both as motor fluctuations well as dyskinesia.

Conclusion

Our results suggest that *DRD1* A48G polymorphism may play a protector effect in the occurrence of dyskinesia in PD patients. Furthermore, we reported findings to strengthen those other variables such as younger age at onset of motor symptoms, disease duration, time of L-DOPA therapy, doses daily of L-DOPA and severity of the disease that can benefit the emergence of motor complications in PD patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest and no competing financial interests.

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