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MAO-B and *COMT* Genetic Variations Associated With Levodopa Treatment Response in Patients With Parkinson's Disease

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Abstract

The most commonly used Parkinson's disease (PD) treatment is the replacement of dopamine by its levodopa precursor (L-dopa). Monoamine oxidase-B (MAO-B) and catechol-o-methyl transferase (COMT) are enzymes involved in the metabolism and regulation of dopamine availability. In our study we investigated the possible relation among selected single-nucleotide polymorphisms (SNPs) in the *MAO-B* (rs1799836) and *COMT* (rs4680) genes and the therapeutic response to levodopa (L-dopa). A total of 162 Brazilian patients from the Pro-Parkinson service of Clinics Hospital of Pernambuco diagnosed with sporadic PD and treated with levodopa were enrolled. PD patients were stratified into 2 groups according to the daily levodopa dose. *MAO-B* and *COMT* SNP genotyping was conducted by polymerase chain reaction–restriction fragment length polymorphism. After multivariate analysis, we observed a significant difference between PD groups for the following variables: sex ($P = .02$), longer duration of disease ($P = .02$), longer levodopa therapy duration ($P = .01$), younger onset of PD ($P = .01$), and use of COMT inhibitor ($P = .02$). We observed that patients carrying *MAO-B* (rs1799836) A and AA genotypes and COMT (rs4680) LL genotype suffered more frequently from levodopa-induced-dyskinesia. In addition, we found an increased risk of 2.84-fold for male individuals carrying the *MAO-B* G allele to be treated with higher doses of levodopa ($P = .04$). We concluded that before beginning PD pharmacological treatment, it is important to consider the genetic variants of the *MAO-B* and *COMT* genes and the sex, reinforcing the evidence that sexual dimorphism in the genes related to dopamine metabolism might affect PD treatment.

Keywords

MAO-B, *COMT*, dyskinesia, levodopa, polymorphisms

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, affecting 1%–2% of the elderly population.[1] By 2030, it is expected that around 8.7 million individuals will suffer from PD.[2] PD etiology is complex, involving both genetic and environmental factors.[1] The main pathological hallmark is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, which leads to alterations in the cortical-striatal-thalamic circuit and, consequently, causes PD symptoms (bradykinesia, resting tremor, postural instability, and rigidity).[3,4]

There is no known effective cure for PD, and the treatment of motor symptoms is based primarily on levodopa use, a dopamine precursor, considered the gold standard treatment for PD. However, individuals undergoing long-term therapy (4–6 years) show a tendency to develop motor complications, such as levodopa-induced-dyskinesia, abnormal involuntary movements and motor fluctuation ("on" periods), and periods during which the medication does not satisfactorily control motor disability and the response is suboptimal ("off " periods).[4,5]

Fahn et al evaluated the adverse effects relative to the daily dose of levodopa and reported that individuals

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receiving the highest dose of the drug had significantly more levodopa-induced-dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo.[6]

Dopamine bioavailability in the central nervous system is associated with the activity of 2 enzymes: monoamine oxidase-B (MAO-B) and catechol-O-methyltransferase (COMT), which are involved in the dopamine inactivation pathway.[4–6] The enzyme COMT is codified by the *COMT* gene, localized at 22q11.21-q11.23, whereas the gene encoding MAO-B is located on the X chromosome (Xp11.4-p11.23).[7,8]

Recent investigations suggest that *COMT* and *MAO-B* single-nucleotide polymorphisms (SNPs) might influence the PD development risk and pharmacological treatment.[9–11] The nonsynonym SNP rs4680 in *COMT,* a G→A transition (valine-methionine substitution) on codon 158 (exon 4) of the membrane-bound transcript variant, has been associated with the modulation of enzyme activity.[11] The A allele was associated with a reduction of 3- to 4-fold in the enzyme activity, being designated as L (low activity), whereas the G allele has been called H because it is associated with higher enzymatic activity.[12] In addition, the *MAO-B* gene contains a single-stranded conformational polymorphism within intron 13 (rs1799836), which results in a transitional conversion of adenine (A) to guanine (G) creating a splicing enhancer, thus changing the enzymatic activity.[13–15]

The impact of genetic variants in the choice of the more adequate PD treatment is still controversial. Thus, it is necessary to search for genetic biomarkers predictive of response to levodopa dose and the development of adverse effects. The present study investigated the possible relationship between the distribution of *MAO-B* and *COMT* functional SNPs and the levodopa therapy effects in PD individuals of a population from northeastern Brazil.

Methods

All the procedures used in this study were evaluated and approved by ethics committee of the Health Ministry of Brazil (CAAE: 45614415.0.0000.5208). Informed written consent from all individuals was obtained, and relevant clinic-epidemiological variables (sex, age of onset, duration of disease, daily levodopa dose, and severity of the disease based on Hoehn-Yahr score)[16] were collected according to a structured questionnaire and medical records in a face-to-face interview with the patients and their family members.

Study Subjects

A retrospective study was performed aimed at investigating the role of *MAO-B and COMT* selected functional genetics polymorphisms in the administration of levodopa in PD patients. A total of 162 PD individuals from a population of northeastern Brazil (Recife) were investigated during the first 5 years of treatment at the PRO-PARKINSON service from the Clinics Hospital of Pernambuco; the idiopathic PD diagnosis was based on the United Kingdom Parkinson's Disease Society Brain Bank criteria.[17] Individuals diagnosed with PD in levodopa treatment were enrolled in this study. However, PD individuals with abnormal symptoms and without levodopa treatment were excluded from the study.

PD patients were classified in 2 groups based on the observation that individuals taking more than 600 mg levodopa tended to develop more adverse effects.[6] The first group consisted of PD individuals treated with a daily levodopa dose equal or below 600 mg/day (group 1); the second group consisted of individuals treated with levodopa doses above 600 mg/day (group 2).

DNA Extraction and Genotyping

Genomic DNA was extracted from 3 mL of 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 Laboratório de Genética Bioquímica e Sequenciamento de DNA Prof[a]. Tânia Falcão at the Universidade Federal Rural de Pernambuco.

MAO-B (rs1799836) and *COMT* (rs4680) variants were genotyped using a polymerase chain reaction–restriction fragment length polymorphism assay following the protocols of Wu et al.[18] A fragment of 217 bp from the *COMT* rs4680 SNP was amplified using the primers 5′-TCGTGGACGCCGTGATTCAGG-3′ and 5′-AGGTCTGACAACGGGTCAGGC-3′ and digested by the restriction enzyme NlaIII, which yields 3 DNA fragments of 40, 81, and 96 bp for the *COMT* A allele (low activity) and 2 DNA fragments of 81 and 136 bp for the *COMT* G allele (high activity). For *MAO-B*, an amplicon of 232 bp was amplified using the primers forward 5′- GGAACCTCTTATACCACAGG-3, and reverse 5′-GACTGCCAGATTTCATCCTC-3′ and digested with the restriction enzyme Tsp45I. *MAO-B* allele 1 (Tsp45I restriction site) was detected when 2 bands of 146 and 86 bp were visible, whereas allele 2 (no Tsp45I restriction site) was detected when a single 232-bp band was visible.[19]

Statistical Analyses

Allele and genotype frequencies were estimated using the software package BioEstat 5.0.[20] Hardy-Weinberg equilibrium was verified for all SNPs using Genotype Transposer software. Univariate analysis and logistic regression were performed using R software

version 3.0.2 (http://www.R-project.org/). The Student *t* test or the nonparametric Mann–Whitney *U* test was used for the assessment of quantitative variables. The Kolmogorov–Smirnov test was used to evaluate normality. The chi-square test and odds ratio were used to compare either allelic frequencies or the genotype frequencies of *MAO-B* or *COMT* genes. Confounders to be included in the multiple linear regression model were determined conceptually or with an association ($P \leq .20$) with levodopa dose and genotypes. The post hoc statistical power analysis was performed with the G*power software (version 3.0.5). A formal Bonferroni correction for the number of analyzed SNPs would require a significance threshold of $P = .025$.

Results

Clinical and epidemiological variables for all PD individuals enrolled in this study are presented in Table 1. Group 1 consisted of 76 PD individuals (46.9%), mostly female sex (40 of 76), with a mean age of 65.2 ± 9.5 years, treated with levodopa doses ≤ 600 mg/day. Group 2 consisted of 86 PD individuals (53.1%), mostly male sex (56 of 86), with a mean age of 63.0 ± 9.3 years, treated with levodopa doses > 600 mg/day.

The male sex was more frequent among PD individuals who were taking >600 mg/day of levodopa ($P = .02$). On average, longer duration of disease and prolonged levodopa therapy were higher in individuals of group 2 (8.1 ± 4.6 and 7.9 ± 4.2 years, respectively) than in group 1 (6.6 ± 4.0 and 6.5 ± 3.8 years, respectively), differing significantly ($P = .02$ and $P = .01$ years, respectively). The mean age at onset (in years) was significantly higher in PD individuals in group 1 (58.6 ± 10.3 years) relative to individuals in group 2 (54.9 ± 10.2 years; $P = .01$). In addition, when we evaluated the concomitant use of other antiparkinsonian drugs, we observed that the majority of PD individuals undergoing COMT inhibitor therapy were in the group taking higher doses of levodopa ($P = 0.02$; Table 1). In addition, PD individuals taking higher daily dose of levodopa (>600 mg/day) showed an association with levodopa-induced dyskinesia ($P = .04$) and motor fluctuations ($P = .01$) compared with the group treated with low doses (Table 1).

The distribution allelic and genotype frequencies of *COMT* and *MAO-B* SNPs among PD individuals treated with high (group 2) and low (group 1) daily levodopa doses is shown in Table 2. When considering allelic and genotypic distribution of *COMT* SNPs, percentage differences were observed, but without reaching statistical significance ($P > .05$).

Because of the location of *MAO-B* on chromosome X, men and women were analyzed separately in the 2 groups (Table 2). The *MAO-B* GG genotype that is associated with increased enzyme activity was more prevalent in the group treated with high daily doses (56.9%) than in the group treated with low daily doses (48.6%). Among women with PD, the GG genotype was more frequent in the low-dose group (47.5%) than in the high-dose group (30.0%). In men who were hemizygotic for the *MAO-B* gene, the G allele was more frequent in the high-dose group (71.4%) than in the low-dose group (50.0%). However, no significant difference was found between groups for *MAO-B* genotype distribution (Table 2).

The *MAO-B* and *COMT* allelic and genotypic distribution was verified for the presence or absence of dyskinesia and motor fluctuation (Table 3). After adjustment by Bonferroni correction, it was observed that PD

Table 1. Association Between Demographic and Clinical Characteristics of Individual With Parkinson's Disease Treated With Low and High Levodopa Doses

Characteristics	Overall n = 162	Group 1 ≤600 mg/day n = 76	Group 2 >600 mg/day n = 86	Univariate Test *P*
Sex (male/female)	(92/70)	(36/40)	(56/30)	.02[a,b]
Age (years), mean ± SD	64.0 ± 9.4	65.2 ± 9.5	63.04 ± 9.3	.12[c]
Duration of disease (years), mean ± SD	7.4 ± 4.4	6.6 ± 4.0	8.1 ± 4.6	.02[a,c]
Levodopa therapy duration (years), mean ± SD	7.2 ± 4.1	6.5 ± 3.8	7.9 ± 4.2	.01[a,c]
Age at onset (years), mean ± SD	56.6 ± 10.4	58.6 ± 10.3	54.9 ± 10.2	.01[a,c]
HY stage ± SD (years)	2.3 ± 0.9	2.2 ± 0.8	2.4 ± 0.8	.16[c]
Antiparkinsonian drug use				
Dopamine agonist use, n(%)	100 (100)	46 (46.0)	54 (54.0)	.64[b]
MAO-B inhibitor use, n(%)	20 (100)	9 (45.0)	11 (55.0)	.85[b]
COMT inhibitor use, n(%)	23 (100)	4 (17.4)	19 (82.6)	.02[a,b]
Amantadine, n(%)	42 (100)	17 (40.5)	25 (59.5)	.42[b]
Adverse effects				
Dyskinesia, n(%)	26 (100)	5 (19.2)	21(80.8)	.04[a,b]
Motor fluctuation, n(%)	69 (100)	21 (30.4)	48 (69.6)	.01[a,b]
Hallucination, n(%)	21 (100)	9 (42.9)	12 (57.1)	.92[b]

[a]Significant *P* value (< .05). OR, odds ratio (OR was only calculated for chi-square test); SD, standard deviation.
[b]Chi-square.
[c]Mann-Whitney test.

Table 2. Distribution of Allele and Genotype Frequencies of *COMT* and *MAO-B* Polymorphisms Within Individuals With Parkinson Disease Treated With High and Low Levodopa Dosage/Daily

Alleles Genotypes	Group 1 ≤600 mg/day n (%)	Group 2 >600 mg/day n (%)	OR (95%CI), *P*
COMT	n = 76	n = 86	
H	99 (65.0)	118 (68.6)	Reference
L	53(34.0)	54 (31.4)	0.8 (0.5–1.3), .58
H/H	30 (39.4)	40 (46.50)	Reference
H/L	39 (51.3)	38 (44.18)	0.7 (0.4–1.4), .43
L/L	7 (9.3)	8(9.32)	0.8 (0.2–2.6), .98
MAO-B			
All	n = 76	n = 86	
G, G/G	37 (48.6)	49 (56.9)	Reference
G/A	14 (18.4)	16 (18.6)	0.8 (0.3–1.9), .89
A, A/A	25 (32.8)	21 (24.4)	0.6 (0.3–1.3), .28
Female	n = 40	n = 30	
G	52 (65.0)	34 (56.6)	Reference
A	28 (35.0)	26 (43.3)	1.4 (0.7–2.8), .40
G/G	19 (47.5)	9 (30.0)	Reference
G/A	14 (35.0)	16 (53.3)	2.4 (0.8–7.0), .17
A/A	7 (17.5)	5 (16.6)	1.5 (0.3–6.0), .82
Male	n = 36	n = 56	
G	18 (50.0)	40 (71.4)	Reference
A	18 (50.0	16 (28.5)	1.5 (0.3–6.0), .63

n, number of Parkinson's disease patients; OR, odds ratio; 95%CI, 95% confidence interval.

$P < .05$ was considered statistically significant.

Table 4. Logistic Regression Model of COMT and *MAO-B* Genotype Influence Over Parkinson´s Disease Patients Treated With High or Low Levodopa Dosages, Adjusted for Clinical Variables

Variables	β	SE	Wald	*df*	*P*	Odds Ratio	95% Confidence Interval Lower	Upper
Age	0.01	0.03	0.284	1	.59	1.01	0.95	1.08
Duration of treatment	0.02	0.05	0.276	1	.59	1.02	0.92	1.13
Age at onset (>59 years)	−0.42	0.64	0.431	1	.51	0.65	0.18	2.30
Female sex	−0.11	0.64	0.030	1	.86	0.89	0.25	3.13
COMT H/L	−0.27	0.40	0.449	1	.50	0.76	0.34	1.69
COMT L/L	−0.98	0.72	1.834	1	.17	0.37	0.09	1.55
COMT inhibitor use	0.89	0.68	1.695	1	.19	2.45	0.63	9.45
Alcohol use	0.72	0.55	1.684	1	.19	2.06	0.69	6.15
Dyskinesia	1.35	0.67	4.066	1	.04[a]	3.87	1.03	14.44
Motor fluctuation	0.74	0.41	3.182	1	.07	2.10	0.92	4.76
MAO-B G/A	0.29	0.65	0.193	1	.66	1.33	0.36	4.86
MAO-B A/A	0.13	0.83	0.024	1	.87	1.13	0.22	5.84
MAO-B G (male)	1.04	0.51	4.120	1	.04[a]	2.84	1.03	7.78
Constant	−1.88	1.99	0.89	1	.34	0.15		

COMT, catechol-O-methyl transferase; *MAO-B*, monoamine oxidase-B; SE, standard error; *df*, degrees of freedom.

$P < .05$ was considered statistically significant.

individuals carrying the A and AA genotypes of *MAO-B* (rs1799836; OR, 2.59; $P = .0139$) and the *COMT* L/L genotype (rs4680; OR, 5.53; $P = .0009$) presented more frequently with dyskinesia, The genotype frequencies in both genes were in accordance with the Hardy-Weinberg equilibrium. Minor allele frequency for the *MAO-B* gene (rs1799836) was 0.39 and for the *COMT* gene (rs4680) was 0.33.

Table 4 shows the results of logistic regression related to clinical and genetic variables of patients that could predict high or low doses of levodopa. The model shows that male patients carrying the *MAO-B G* allele (rs1799836; OR, 2.84; $P = .04$) and/or presenting with

Table 3. Genotypic Distribution of *MAO-B* and *COMT* Polymorphism in Individuals With Parkinson's Disease in the Presence or Absence of Adverse Effects, Dyskinesia, and Motor Fluctuation

	Dyskinesia, n = 150				Motor Fluctuation, n = 150			
Gene/Variations	Present (n = 26)	Absent (n = 124)	*P* Adjusted	OR (95%CI)	Present (n = 69)	Absent (n = 81)	*P* Adjusted	OR (95%CI)
MAO-B (rs1799836)								
G/G,G	34.6% (9)	57.2% (71)		Reference	55.1% (38)	51.8% (42)		Reference
G/A	30.8% (8)	15.3% (19)	.01[a]	9.0 (1.5-52.8)	18.8% (13)	17.3% (14)	.58	1.5 (0.5–4.3)
A/A,A	34.6% (9)	27.5% (34)		2.5 (0.8 -7.6)	26.1% (18)	30.9% (25)		0.8 (0.3–1.7)
COMT (rs4680)								
H/H	50% (13)	40.6% (50)		Reference	43.4% (30)	40.7% (33)		Reference
H/L	19.3% (5)	53.6% (67)	.0001[a]	0.2 (0.09-0.8)	46.4% (32)	49.3% (40)	.91	0.8 (0.4–1.7)
L/L	30.7% (8)	5.8% (7)		5.5 (1.5-20.1)	10.2% (7)	9.9% (8)		0.9 (0.3–2.9)

n, number of Parkinson´s disease individuals; OR, odds ratio; 95%CI, 95% confidence interval.

[a]$P < .05$ statistically significant.

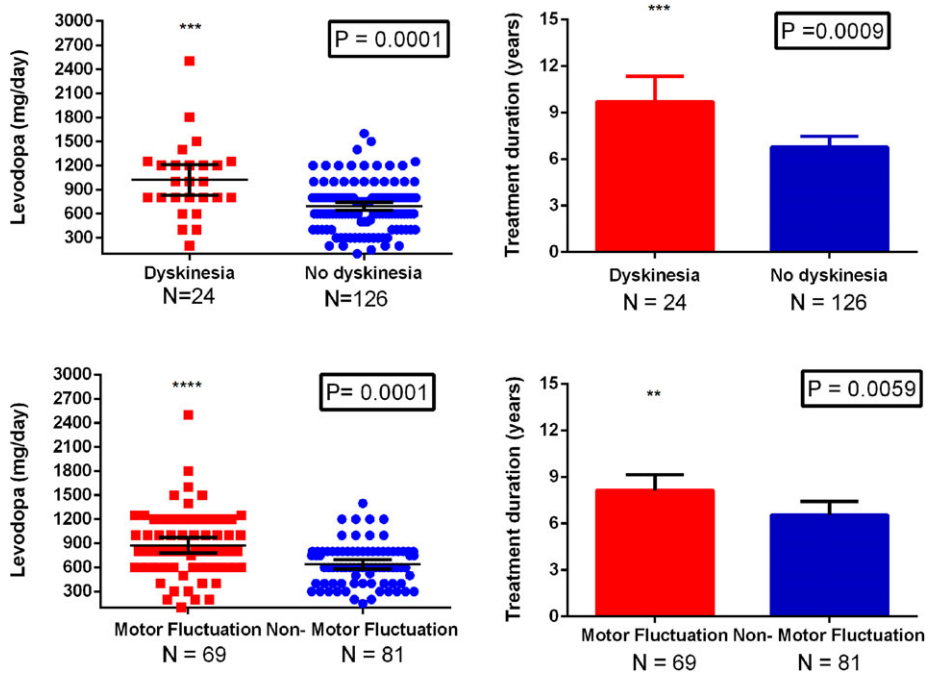

Figure 1. Correlation of motor complications and levodopa treatment parameters in PD patients. N, number of patients. Red bars and plots represent patients with adverse effects, and blue bars and plots indicate those without adverse effects. Data show median and 95% confidence intervals. *P* value is of unpaired *t* test with Welch's correction.

dyskinesia (OR, 3.87; $P = .04$) were those treated with higher doses of levodopa.

Discussion

Motor complications such as levodopa-induced-dyskinesia and motor fluctuation are undesirable consequences of PD treatment and severely affect the quality life of patients.[7] In our study we observed that the development of these symptoms correlated with disease duration and levodopa dosage (Figure 1), as already shown in the literature.[21] Because PD is a neurodegenerative and progressive disease, it is inevitable that these parameters have a role in disease progression. For that reason, the identification of new biomarkers predicting disease progression is a priority in the PD clinical context.

In this study we evaluated whether the functional genetic variability of genes coding for levodopa-metabolizing enzymes (*COMT* and *MAO-B)* might influence the response to levodopa in PD individuals as well as the development of side effects after treatment. The *COMT* L/L genotype (rs4680) and *MAO-B* A/A genotype (rs1799836) were associated with risk of dyskinesia developing after adjusting for sex and age (Table 3), suggesting that variants related to low enzymatic activity of these enzymes could affect the dopamine pathway, with defective inactivation and consequent accumulation of dopamine in the synaptic cleft, resulting in an increase in levodopa in plasma and leading to peak-dose dyskinesia. Other studies also found the same result related to the *COMT* L/L genotype and levodopa-induced-dyskinesia susceptibility; however, they were not able to reach statistical significance after Bonferroni's correction.[22,23]

When we analyzed the group of PD individuals as a whole, we observed that individuals with advanced disease time, as well as those who had an earlier onset, were associated with high levodopa daily doses. Similar to our findings, Altmann et al[24] also described an association between major disease progress and high doses of levodopa. Two examples of evidence may support this finding: (1) levodopa treatment does not have a protective effect on PD progression, and so far, nothing can be done to slow down the degenerative process and the loss of dopaminergic neurons[25]; and (2) the MAO-B enzyme is responsible for oxidative stress in the substantia nigra, and its activity increases with age. Thus, it is probable that increased MAO-B activity contributes to neurodegeneration and consequently a need for more dopamine.[26]

Our data showed that PD individuals carrying the *COMT* H/H genotype have a tendency to need higher doses of levodopa. In a previous study conducted by Bialecka et al,[9] an association between high daily doses of levodopa and the haplotype block formed by 4 *COMT* SNPs related to high enzymatic activity was described. Furthermore, in the present study the *COMT* LL genotype (lower enzymatic activity) was more frequent in the group treated with higher doses

compared with the group treated with lower doses (2.8%), but no significant difference was found, suggesting that the *COMT* rs4680 has no relation to the daily dose of L-dopa.

The other gene participating in dopamine metabolism is *MAO-B*, which also may be involved in sex-related differences in the clinical outcome of PD. Some studies reported a possible association between PD susceptibility and variations in the X chromosome, which may explain the higher incidence of PD among men.[27]

The A644G SNP of the *MAO-B* gene, localized at intron 13, creates a splicing enhancer site that modifies the enzymatic activity, but which allele confers higher or lower activity remains unclear.[28] Balciuniene et al[29] reported increased MAO-B brain enzyme activity in the presence of the *MAO-B* A allele compared with the G allele. In contrast, Garpenstrand et al[30] and Costa-Mallen et al[31] observed that the *MAO-B* G allele was associated with increased MAO-B activity in platelets and cultured cells. Torkman-boutorabi et al[13] and Białecka et al[32] found an increased tendency of the need for high doses of levodopa in individuals carrying the *MAO-B* G/G genotype.

In our study, no statistically significant difference was observed between high and low dosage of levodopa when using univariate analysis. For that reason, further studies on *MAO-B* gene expression are needed to elucidate the role of the *MAO-B* rs1799836 polymorphism in the modulation of enzyme activity.

In addition, among the logistic regression and univariate analyses, we found a 2.84-fold increased risk of male individuals with PD carrying the *MAO-B* G allele to be treated with high doses of levodopa ($P = .04$), suggesting a possible correlation of the genetic variant with sex on levodopa treatment, reinforcing the evidence that a sexual dimorphism of the genes related to dopamine metabolism may exist.

Conclusion

Based on our findings, we concluded that before treating PD patients with levodopa, it is important to take into consideration the genetic variants of the *MAO-B* and *COMT* genes and sex, emphasizing that sexual dimorphism of the genes related to dopamine metabolism might affect PD treatment.

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Declaration of Conflicting Interests

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

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