



Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Dopaminergic polymorphisms associated with medication responsiveness of gait in Parkinson's disease

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ARTICLE INFO

Article history:

Received 14 September 2017

Received in revised form

3 December 2017

Accepted 11 December 2017

Keywords:

Parkinson's disease

Gait

Individual/subgroup differences

DRD2

Dopaminergic medication responsiveness

ABSTRACT

Background: Gait dysfunction is a common symptom of Parkinson's disease that can cause significant disability and put patients at risk for falls. These symptoms show variable responsiveness to dopaminergic therapy.

Objective: To determine whether dopaminergic (rs1076560 *DRD2* G > T and rs4680 catechol-O-methyltransferase (*COMT*) Val158Met) or brain derived neurotrophic factor (rs6265 *BDNF* Val66Met) genetic polymorphisms are associated with gait function and medication responsiveness in Parkinson's disease.

Method: Gait function was evaluated on two days for patients (ON and OFF medication in a counter-balanced fashion) and a single session for controls. Investigators were blinded to genotype during data collection. Associations between genotype and medication responsiveness were analyzed using mixed model ANOVAs. A priori hypotheses were tested using GAITrite[®] electronic mat spatiotemporal gait parameters including step length, step width, velocity, portion of double and single support per gait cycle, and variability of these measures ON and OFF medication.

Results: We found that the *DRD2* polymorphism, but neither *COMT* nor *BDNF*, was consistently associated with gait function and medication responsiveness in the patients. Specifically, Parkinson's disease patients with reduced striatal D2 expression (*DRD2* T allele carriers) had worse gait dysfunction and showed greater dopamine responsiveness of gait function compared to patients who were homozygous for the G allele. There was no effect of any of the genetic polymorphisms on gait for controls.

Conclusions and relevance: The findings suggest that genetic subgrouping, in particular for *DRD2*, may be used to identify Parkinson's disease patient subgroups that are more dopamine responsive for gait function.

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1. Introduction

Gait dysfunction in Parkinson's disease is characterized by slow,

shuffling steps, postural changes and reduced arm swing. These symptoms present early in the disease, increase risk for falls, and potentially cause significant disability [1]. The gait in Parkinson's disease is less responsive to dopaminergic medications and surgical interventions than other symptoms [2], suggesting that dopaminergic denervation may not entirely modulate gait dysfunction [2,3]. Some recent studies have linked Parkinson's disease gait dysfunction to cholinergic denervation (cf [3]), while others have

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shown that some gait parameters improve with dopaminergic treatment [2,4]. Individual differences may explain, at least in part, this rather mixed literature on the medication responsiveness of Parkinson's disease gait.

We previously reported that the single nucleotide polymorphism (SNP) rs1076560 in the dopamine D2 receptor (*DRD2*) gene is associated with the magnitude of L-DOPA improvements in motor sequence learning in Parkinson's disease patients; L-DOPA improved learning only in patients carrying the minor T allele [5]. These findings have potential implications for clinical treatment decisions, but genetic associations with L-DOPA responsiveness for more clinically relevant behaviors such as locomotion have been evaluated in only one study. This study found that genotype for the dopamine transporter gene *SLC6A3* was associated with Unified Parkinson's Disease Rating Scale (UPDRS) motor score and gait responsiveness to both an acute L-DOPA challenge and 90 days of methylphenidate treatment [6]. These patients were all implanted with deep brain stimulators, however, raising the question of whether less severely affected patients would also show similar gene-medication associations.

In the current study, we evaluated whether the genetic polymorphisms *COMT* Val158Met (rs4680), *DRD2* G > T (rs1076560) and *BDNF* Val66Met (rs6265) would predict medication responsiveness of gait function in Parkinson's disease. The *COMT* SNP (rs4680) regulates dopamine availability in the prefrontal cortex and corticostriatal circuits [7]. A substitution of the valine (Val) with methionine (Met) allele at this codon reduces *COMT* enzymatic activity, resulting in higher prefrontal dopamine availability [8]. *COMT* genotype has been associated with gait speed in healthy older adults [9]. The *DRD2* G > T polymorphism (rs1076560) influences dopamine availability by regulating striatal dopamine receptor expression. Healthy T allele carriers—who have reduced D2 receptor expression—often perform worse on cognitive and motor tasks [10,11]. We also evaluated the *BDNF* Val66Met polymorphism (rs6265) that regulates *BDNF* secretion. Met allele carriers frequently show reduced short-term brain plasticity and worse performance on motor learning tasks [12]. Moreover, *BDNF* protein is associated with dopamine release and uptake *in vitro* [13,14].

Here, we analyzed gait parameters in Parkinson's disease patients, both ON and OFF antiparkinsonian medication, and controls. We evaluated the association between the genetic variants *COMT* Val158Met (rs4680), *DRD2* G > T (rs1076560) and *BDNF* Val66Met (rs6265) and Parkinson's disease gait dysfunction and medication responsiveness.

2. Materials and methods

2.1. Experimental design

We tested the effects of antiparkinsonian medications on gait parameters while patients walked at their fastest, preferred, and slowest speeds. For clinical relevance, we present only the

preferred walking speed data but results for the other conditions were qualitatively similar. We evaluated whether medication responsiveness of gait parameters was associated with genotype for the *COMT* Val158Met, *DRD2* G > T, and *BDNF* genetic polymorphisms.

2.2. Participants

Thirty-nine Parkinson's disease patients and 30 healthy volunteers participated. We excluded participants with known neurological or psychiatric diseases other than Parkinson's disease, who were not taking dopaminergic antiparkinsonian medication(s) or who had undergone surgery for deep brain stimulation.

A movement disorder specialist diagnosed patients with idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [15]. All patients had mild-to-moderate stage Parkinson's disease. Patients' antiparkinsonian medications were heterogeneous; several patients took DA agonists alone or in combination with other antiparkinsonian medications (levodopa+ = 50%, levodopa+ & dopamine agonist = 27.78%, dopamine agonist only = 16.67%, monoamine oxidase B inhibitor only = 5.56%). We evaluated Parkinson's disease motor severity with the Movement Disorder Society's Unified Parkinson's Disease Rating Scale [MDS-UPDRS; 16]. Additionally, all participants completed the Montreal Cognitive Assessment (MOCA; [17]). Table 1 provides participant characteristics. The experiment was conducted in accord with the Declaration of Helsinki and was approved by the Institutional Review Board. All participants provided written, informed consent.

Gait data from four patients were removed from analyses due to: MOCA scores suggestive of dementia [$n = 1$; 17], a recent medication change (<six months; $n = 1$), a recent knee surgery ($n = 1$), and abnormal neurological findings on examination ($n = 1$). Analyses were performed on the remaining data from 36 patients (10 females) and 29 controls (16 females). Two control participants declined to consent to genotyping and were not included in the genotype analyses.

2.3. Genotyping

We obtained saliva samples using an Oragene DNA self-collection kit. Genotyping was performed using a polymerase chain reaction following previously published protocols [11]. The SNPs for rs4680, rs1076560 and rs6265 were determined. The distributions of individuals within each genotype group are presented in esupp Table 1; these were in accord with an exact test of the Hardy-Weinberg equilibrium [$ps > .09$; 18].

2.4. Apparatus

We used a GAITRite® electronic mat to collect gait parameters (CIR Systems, Inc., Sparta, NJ) using GAITRite® Software (Version

Table 1
Participant characteristics.

	Age (years)	Education (years)	MOCA		Years Diagnosed	MDS-UPDRS		LED (mg)
			ON	OFF		ON	OFF	
Parkinson's disease	67.46 ^a (8.40)	16.44 ^c (3.00)	27.11 ^d (2.71)	26.92 ^d (2.23)	5.07 (3.38)	30.64 (9.08)	35.00 (10.88)	517.24 (323.91)
Controls	62.90 ^b (5.28)	16.86 ^c (2.92)	—	27.17 ^d (2.51)	—	—	—	—

Note. Values in parentheses are standard deviations. Abbreviations: — = No Data; Parkinson's disease-Specific Measure; MDS-UPDRS = Movement Disorder Society's-Unified Parkinson's Disease Rating Scale (Motor Section); MOCA = Montreal Cognitive Assessment; LED = L-DOPA Equivalency Dose [23]. Group comparisons with the same superscript are not significantly different.

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