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Dopamine receptors and BDNF-haplotypes predict dyskinesia in Parkinson's disease

Cynthia DJ Kusters, MD[1,*], **Kimberly C Paul, MPh, PhD**[1], **Ilaria Guella, PhD**[2], **Jeff M Bronstein, MD, PhD**[3], **Janet S Sinsheimer, PhD**[4,5], **Matt J Farrer, PhD**[2], and **Beate R Ritz, MD, PhD**[1,3,6]

[1]Department of Epidemiology, UCLA Fielding School of Public Health, Los Angeles, CA, USA

[2]Department of Medical Genetics, Centre for Applied Neurogenetics, University of British Columbia, Vancouver, BC, Canada

[3]Department of Neurology, David Geffen School of Medicine, Los Angeles, CA, USA

[4]Department of Biostatistics, UCLA Fielding School of Public Health, Los Angeles, CA, USA

[5]Department of Human Genetics and Biomathematics, David Geffen School of Medicine, Los Angeles, CA, USA

[6]Department of Environmental Health, UCLA Fielding School of Public Health, Los Angeles, CA, USA

Abstract

Objective—Dyskinesia is a known side-effect of the treatment of Parkinson's Disease (PD). We examined the influence of haplotypes in three dopamine receptors (*DRD1*, *DRD2* and *DRD3*) and the Brain Derived Neurotrophic Factor (*BDNF*) on dyskinesia.

Methods—Patient data were drawn from a population-based case-control study. We included 418 patients with confirmed diagnoses by movement disorder specialists, using levodopa and a minimum three years disease duration at the time of assessment. Applying Haploview and Phase, we created haploblocks for DRD1-3 and BDNF. Risk scores for *DRD2* and *DRD3* were generated. We calculated risk ratios using Poisson regression with robust error variance.

Results—There was no difference in dyskinesia prevalence among carriers of various haplotypes in *DRD1.* However, one haplotype in each *DRD2* haploblocks was associated with a 29 to 50%

[*]Corresponding author: Cynthia Kusters, MD., Ph.D. Candidate, Department of Epidemiology, University of California, 650 Charles Young Drive South, Los Angeles, California, 90095, USA. Phone: (310) 206 – 7458. cynthiakusters@gmail.com.

Author Contributions: Jeff M Bronstein has evaluated the majority of patients to evaluate their Parkinson's disease status and symptoms; Ilaria Guella and Matt J Farrer were responsible for the genetic analysis and quality control; Matt J Farrer and Beate R Ritz were responsible for the conception, and overseeing the organization and execution; and the analysis were primarily performed by Cynthia DJ Kusters with the help of Kimberly C Paul, Janet S Sinsheimer and Beate R Ritz. The first draft of the article was written by Cynthia DJ Kusters. All of the authors contributed to the inference of the results from the analysis, the editing and writing of the paper.

Conflicts of Interest: None

increase in dyskinesia risk. For each unit increase in risk score, we observed a 16% increase in dyskinesia risk for *DRD2* (95%CI: 1.05-1.29) and a 17% (95%CI: 0.99-1.40) increase for *DRD3*. The *BDNF* haploblock was not associated, but the minor allele of the rs6265 SNP was associated with dyskinesia (adjusted RR 1.31 (95%CI: 1.01-1.70)).

Conclusion—Carriers of *DRD2* risk haplotypes and possibly the *BDNF* variants rs6265 and *DRD3* haplotypes, were at increased risk of dyskinesia, suggesting that these genes may be involved in dyskinesia related pathomechanisms. PD patients with these genetic variants might be prime candidates for treatments aiming to prevent or delay the onset of dyskinesia.

Keywords

Parkinson's disease; dyskinesia; DRD1-3 and BDNF genes; haplotypes

Introduction

Parkinson's disease (PD) leads to significant disability and loss of quality-of-life.[1] One important component to loss of quality-of-life is L-dopa-induced dyskinesia, a common side-effect of treatment. Dyskinesia affects 25% within the first five years [2] increasing up to 80% among patients ten years into disease.[3] Dyskinesia is associated with depression and increases health-related costs.[4] Interestingly, although some patients develop dyskinesia early in their disease, other patients never do.

The two basal ganglia circuitry pathways (D1 and D2) associated with movement control are regulated by dopamine receptors. Common genetic variations in *DRD* loci are natural candidates for dyskinesia risk.[5,6] In addition, Brain Derived Neurotrophic Factor (*BDNF*) may affect dyskinesia due to modulation of dopamine receptor expression.[7,8]

The majority of studies focused on *DRD1-3* and *BDNF*. Many of these have concentrated on SNPs only, specifically the rs1800497 in *DRD2*,[9–17] the rs6280 in *DRD3*,[11,13,18] and the rs6265 in *BDNF*.[9,19,20] The results from these studies have reported inconsistent results.[9–20] One small clinic-based study using a Brazilian population, analyzed *DRD2* haplotypes (based on rs228365, rs1076560, rs6277, rs1800497 and rs2734849) and implicated that *DRD2* haplotypes are associated with dyskinesia.[14]

Here we are using a targeted approach for the three dopamine receptors (*DRD1-3*) and *BDNF*, to estimate risk of dyskinesia based on haplotypes' variants. Reviewing haplotypes instead of SNPs limits the number of tests and allows us to examine gene regions. Patients were enrolled in our large population-based study in California (N=747) and dyskinesia was assessed relatively early, on average five years after first diagnosis based on cardinal motor symptoms.

Methods

Study population

We assembled a cohort from the population-based case control study Parkinson's Environment and Gene (PEG) study, which enrolled and followed patients from three

Central California counties (Kern, Fresno, and Tulare) between 2001 and 2015. All patients were seen by movement disorder neurologists (JB, Dr. Bordelon) at least once at baseline, many on multiple follow-up occasions, and were confirmed as having probable idiopathic PD according to published criteria.[21] Recruitment occurred in two phases. Recruitment during the first phase (PEG1) in 2001-2007 has been described before.[22] Among 563 potential patients, 359 incident PD patients within the first three years after diagnosis were identified at baseline. Dyskinesia was assessed during the first follow-up appointment, where we saw 250 PEG1 patients at least once. The second recruitment strategy (PEG2) ensued during 2010-2015 and identified 388 idiopathic PD patients (from 589 potential patients). In PEG2, patients were allowed to have received a PD diagnosis after 2001.

Disease duration was measured from the date of diagnosis to the time of the Unified Parkinson's disease Rating Scale (UPDRS) IV assessment. We restricted our population to those taking levodopa (N=459; 193 PEG1 and 266 PEG2 subjects). As dyskinesia is unlikely to develop within the first years after diagnosis, we further restricted our analysis to patients seen with a minimum of three calendar years of disease duration. Among patients who were seen too early in disease (N=101) or were not taking levodopa medication (N=143) at the first assessment, we examined whether they met our criteria during a second assessment (34 PEG1; 26 PEG2). Supplemental figure e-1 provides a flow diagram for the study population of 418 PD patients included in our final analyses.

All study protocols regarding human subjects in PEG1 and PEG2 have been approved by the local Institutional Review Board and all participants gave their written informed consent.

Definition of outcome and other variables

Dyskinesia was assessed during follow-up visits in PEG1, and starting with the first visit in PEG2 (for some patients dyskinesia was assessed shortly after their first contact) using the UPDRS part IV.[23] Dyskinesia presence was noted (yes/no) and the severity of dyskinesia was measured in hours per day (no dyskinesia, ≤25%, 26-50%, 51-75% and >75% of the waking day).

Based on Parkinson's medication at the dyskinesia assessment, we calculated a levodopa-equivalent daily dosage (LEDD) converting all reported anti-Parkinsonian medications into a standardized equivalent dosage according to a previously described algorithm.[24] Race/ethnicity was established via genetic Ancestry Informative Markers (AIMS) if available (72.5% of those included here) or by self-report of ancestry if AIMS markers had not been measured (27.5%). We grouped race/ethnicity as European ancestry, Hispanic and other.

Genetic analysis

DNA was extracted at UCLA from whole blood and genotyping was conducted at UBC for all patients with a confirmed diagnosis of PD. A total of 26 SNP were selected to be genotyped across the three DRD genes: 5 SNPs for *DRD1*, 12 SNPS for *DRD2*, 8 for *DRD3* loci (supplemental table e-1). Markers were mainly selected for haplotype tagging. Genotyping was performed in duplicate at UBC using a Sequenom MassARRAY platform and custom iPLEX assay. Three SNPs in the *BDNF* locus were previously genotyped at UCLA for a subset of the study sample (N=312 patients with PD). All SNPs had a

genotyping call rate >97%, MAF>5% and were in Hardy-Weinberg equilibrium (as defined by a p-value greater than 0.01 in Caucasians) except for rs11030104 (p-value: $1.7*10^{-9}$), which was subsequently excluded.

Using Haploview,[25] we created linkage disequilibrium (LD) plots based on the total study population (supplemental figure e-2). A haploblock, based on several SNPs, consists of various haplotypes, i.e. SNP patterns. Haploblocks were created based on the confidence intervals.[26] The haplotypes with the highest probabilities for each subject were generated with Phase v2.1.1; rare haplotypes with a frequency of less than 30 patients (=3.7%) were combined into one subgroup.[27] We created one haploblock for the *BDNF*- and *DRD1*, and three haploblocks for *DRD2* and *DRD3* loci (supplemental figure e-2). The haplotypes in the three haploblocks are correlated. For the *DRD2* haploblocks, the D' between the first and second haploblock is 1.0, and between the second and third 0.25. For *DRD3*, the D' between the first and second haploblock is 0.94 and between the second and third haploblock 0.61. The BDNF haplotype consisted of only two SNPs; the R-squared was 0.19 and D-prime was 1.0.

Statistical methods

All analyses were performed using SAS 9.4 (SAS Institute, Cary NC). We estimated risk ratios (RR) using Poisson regression models with robust error variance and a log link function[28] to estimate effects for eight chromosomal regions in four genes on dyskinesia occurrence. The analyses were adjusted for gender, PEG recruitment period, disease duration, LEDD, race/ethnicity and age at diagnosis. Throughout, we adjust for LEDD, adjusting for L-DOPA daily dosage instead produced the same results. For analyses of dyskinesia severity, we distinguished three categories [no, mild (<25%) and moderate/severe (>25%)] to ensure that the proportional odds assumption of our model was met. When multiple haploblocks in one gene showed associations, we created a risk score summing across the three risk-haplotypes and estimated the effect according to the number of risk haplotypes a patient carried.

Finally, we assessed whether individual SNPs alone could explain the associations by analyzing each SNP independently. In sensitivity analyses, we examined whether results were consistent across race/ethnicity by restricting participants to their ancestry.

Results

Patient characteristics

The prevalence of dyskinesia in our patient sample was 24.6%, with the majority experiencing symptoms of dyskinesia less than 25% of their waking hours per day. The average age at diagnosis was 67 years, and on average 5.5 calendar years had passed since first diagnosis when we assessed dyskinesia in our study (see table 1). Haplotype frequencies ranged between 4 and 51% in our haploblocks (supplemental figure e-2). The *BDNF* haplotype had a minimum frequency of 18.9% and a maximum of 45.4%. Because haploblock 2 of the *DRD3* loci consists almost exclusively of the GG haplotype, we lacked

statistical power to examine associations for this block. This haploblock was therefore omitted from analyses.

Dyskinesia risk decreased with increasing age of PD diagnosis (with each year increase in age at diagnosis: RR=0.98 (95% CI: 0.96-0.99), increased with LEDD (per 1000 mg: RR=1.77 (95% CI: 1.29-2.44), increased with disease duration (per calendar year: RR=1.14 (95%CI: 1.07-1.21); and increased with UPDRS score (per five units increase: RR=1.07 (95%CI: 1.01-1.14)). Gender, years of schooling, smoking status, family history of PD, and ethnicity were not associated with dyskinesia in our population sample. The effect sizes and confidence intervals were very similar for the association among these variables with 'severity of dyskinesia'.

Association haplotypes with dyskinesia and 'severity of dyskinesia'

We did not find any association between dyskinesia or 'severity of dyskinesia' and haplotypes for *DRD1.* For *DRD2*, in both adjusted and unadjusted analyses, we found all three *DRD2*-haploblocks to be associated with dyskinesia. We adjusted for gender, PEG1 or 2 recruitment, disease duration, LEDD, race/ethnicity and age at diagnosis. In each haploblock there was one haplotype that accounted for about a 29 to 50% increased risk for dyskinesia. For 'severity of dyskinesia', the effect sizes were slightly higher (33-62% increase) and 95% confidence intervals (CIs) were narrower. For *DRD3*, the TGG-haplotype of the first haploblock and the CC-haplotype of the third haploblock suggested an increase in risk of developing dyskinesia, however the 95% CIs included the null value. Finally, for *BDNF*, the TA-haplotype was associated with 'severity of dyskinesia' with an increase of 43%, however the effect estimate for presence of dyskinesia did not reach statistical significance in our data (see tables 2 and 3).

Combining "risk haplotypes" (defined as the haplotypes in each haploblock associated with increased risk for dyskinesia) into a risk-score for the DRD2 (see supplemental table e-2 for prevalence of risk-scores), we estimated a 16% risk increase for dyskinesia and 21% risk increase for 'severity of dyskinesia' with each unit increase in risk score. Analyzing the risk score as a categorical variable, there is also a clear increase in odds with an increasing risk score. Compared to no risk haplotypes, having 1 to 3 risk haplotypes increases the risk by about 55%, while having 4 or more haplotypes increases the risk by 153%. The risk score for the *DRD3* showed an increase of 17% with each additional "risk haplotype" and a 20% increase for 'severity of dyskinesia', though both confidence intervals included or were very close to the null. However, we observed a dose-response pattern when reviewing the association with the risk score as a categorical variable (see table 4).

Restricting the sample to patients of European ancestry did not change the results for dyskinesia nor for 'severity of dyskinesia'. None of the individual SNPs were responsible for the haplotype findings in the *DRD* loci. However, in *BDNF*, the rs6265 SNP was associated with dyskinesia (aRR: 1.31 (95%CI: 1.01-1.70; p:0.04)), while the rs11030101 was not (aRR: 0.96 (95%CI: 0.74-1.26); p:0.78). Risk among minor allele carriers of rs6265 was even more pronounced for 'severity of dyskinesia' (aRR: 1.43 (95%CI: 1.10-1.97); p: 0.01).

Discussion

In our large community-based study of PD conducted in central California, we estimated an increased odds for developing dyskinesia after dopaminergic treatment in specific *DRD2*, *DRD3*, and *BDNF* but not *DRD1* haplotype carriers. Our study finds that genetic variation in *DRD2* influences the prevalence of dyskinesia and its severity in a dose response manner. Some variations in *DRD3* and *BDNF* may further contribute to the risk and "severity of dyskinesia". Our findings proved robust in sensitivity analyses. The three *DRD2* "risk haplotypes" are frequently prevalent in the population (supplemental figure e-2 and table e-2). Hence, a large percentage of L-dopa treated patients are at increased risk of developing dyskinesia. Overall, about 30% of subjects have no *DRD2* risk haplotype, with about 60% having one to three risk haplotypes; and about 10% carrying four or more risk haplotypes. Especially patients with more than three risk haplotypes are at a much higher risk since the risk of dyskinesia in medicated patients increased by 153%.

We chose to not use a correction for multiple testing, because the four genes in this study were chosen based on previous findings and because the haplotypes within each gene are highly correlated. However, when using an excessively restrictive Bonferroni correction assuming 10 tests (8 haplotypes and 2 risk scores) leading to an alpha value of 0.005, our findings for the *DRD2* risk score would still be considered statistically significant. Only one previous study investigated an association between haplotypes in *DRD2* and dyskinesia. The haplotypes in this relatively small Brazilian clinic-based population (N=199) were generated from different SNPs.[14] Our SNPs were chosen based on tagging characteristics rather than to replicate this previous study. Even though we cannot compare our results directly to these haplotypes, several SNPs are in LD with ours. Specifically, rs6277 and rs2734849 are associated with the rs1089154 and rs1554929 from our first haploblock (R-square is 1.0 for rs6277 and 0.77 for rs2734849) based on HapMap data. Furthermore, rs2283265, rs1076560 and rs1800497 are associated with the rs2471857 and rs2471854 from our second haploblock with R-squares of 0.98, 0.94 and 0.64, respectively. According to functional studies, the rs1800497 is associated with a decrease in *DRD2* expression.[29] Thus, our haploblock may be associated with functional changes in *DRD2* expression.

Previous studies reviewed the association between *DRD3* and dyskinesia, focusing mainly on the rs6280 SNP (Ser9Gly).[11,13,18] The particular Ser9Gly polymorphism in the dopamine 3 receptor has a higher binding affinity to dopamine,[30] and is in high LD with our third haploblock (R-square for rs226082 and rs324026 are 0.84 and 1.00, respectively). Although one Korean study found an association with a small subgroup of patients with diphasic dyskinesia,[13] other studies showed no association with dyskinesia.[11,18] Unfortunately, we did not gather information about the type of dyskinesia and cannot stratify our patients according to subtypes. The estimated effect size for *DRD3* in our study is smaller than for *DRD2* limiting our power to identify a statistically significant finding. However, our findings suggest that the *DRD3* haplotypes may be relevant for dyskinesia, even though they are not formally statistically significant.

In our study, the rs6265 SNP of *BDNF* was associated with dyskinesia while haplotype associations were not evident. The minor allele of SNP rs6265 (Val66Met) has been

previously associated with time to development of dyskinesia in a study of 315 patients from the Cambridge Centre for Brain repair.[20] Yet another study involving 285 Australian patients with PD did not find any difference in time to onset of dyskinesia. [19] The minor allele of rs6265 is associated with a change of valine to methionine at codon 66 causing decreased protein secretion. This change has been used as a biologic argument for increased susceptibility for dyskinesia.[6]

In genetic studies, an important potential confounder is race/ethnicity. To avoid potential population stratification, we limited our analyses to patients from European ancestry in sensitivity analyses and our findings did not change. We adjusted our analysis for race/ethnicity according to three categories. Primary analyses were not adjusted for population substructure using fractional ancestry because AIMs were not available on ~25% of the individuals. However, when we limited our analysis to those individuals with AIMs and adjusted for population structure, we got essentially the same results (results not shown). Race/ethnicity in our study was based mostly on genetic AIMS markers, or – if unavailable – on self-report of parental origin. The correlation between these two measures is high (95.4%) in our population. Although there may be some measurement error for race/ethnicity, based on self-report, there is no indication this would unduly influence our findings.

Information on dyskinesia on almost all subjects was available though we did not assess dyskinesia during the baseline examination early in disease for subjects enrolled in PEG1. A third of all patients were lost to follow up between baseline and follow-up exam in PEG1. The main reason for this was mortality and disease severity preventing participation. Thus, if both dyskinesia and genetic variants of interest influence mortality, we may have a survival bias in PEG1 subjects. However, as findings were consistent across both studies (PEG1 and PEG2) and dyskinesia was assessed in PEG2 subjects at baseline such a survival bias appears unlikely. We only gathered information about dyskinesia prevalence at the time of motor function assessment during physical examinations and we did not record the exact start time of dyskinesia leading to left censoring. This limitation does not allow us to conduct a time-to-event analysis. However, most of the PEG patients were early in their presentation (on average 5.1 years at first dyskinesia assessment) and were followed up within 2-5 years of the first dyskinesia assessment.

The presence of one of the risk haplotypes, or variant alleles, can have major implications for best practices in treatment of PD. Patients who are at higher risk for developing dyskinesia may benefit from therapy with dopamine agonists along with a more strict L-dopa-sparing strategy. Treatment plans should reflect the difficulty in managing PD, to maximize optimal effects (L-dopa ‘on’ time) but also mitigate dyskinesia risk. Our results suggest that individual treatment plans should consider a patient's genetic profile.

Conclusion

Several haplotypes in *DRD2*, possibly haplotypes in *DRD3* and the minor allele of rs6265 in *BDNF*, increased the risk of dyskinesia in our study. Levodopa induced dyskinesia and PD symptoms must be approached as a tradeoff. Nevertheless, genetic information may help prevent or postpone this debilitating consequence of treatment and may improve patient-

centered, personalized therapy. Association studies require confirmation and the health care economy of implementing more personalized treatment should also be quantified before decisions are made. PD patients with these specific risk haplotypes may be prime candidates for testing approaches to prevent or delay the development of dyskinesia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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In addition, M. Farrer has a patent on genetic variability in LRRK2 and Parkinson's disease (US8409809, US8455243B2) and on LRRK2 mouse models that have been subsequently developed, with royalties paid through Mayo Foundation.

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Highlights

- Dopamine receptor genes (DRD1-3) and Brain Derived Neurotrophic Factor (BDNF) have been proposed to be involved in the development of dyskinesia

- *DRD2* haplotypes, and potentially *DRD3* haplotypes and rs6265 *BDNF*-SNP, were associated with dyskinesia

- The subpopulation of patients with these genetic markers appear prime candidate for testing approaches to prevent or delay the development of dyskinesia

Table 1

Overview of characteristics of the PEG study population

	Dyskinesia		No Dyskinesia		Total sample population	
	Total N	**N=103 %**	**Total N**	**N=315 %**	**Total N**	**N=418 %**
Race						
European ancestry	87	84.5	244	77.5	331	79.2
Hispanic	14	13.6	60	19.0	74	17.7
Other	2	1.9	11	3.5	13	3.1
Smoker						
Non-smoker	58	56.3	171	54.3	229	54.8
Former smoker	43	41.7	138	43.8	181	43.3
Current smoker	2	1.9	6	1.9	8	1.9
Gender						
Male	62	60.2	207	65.7	269	64.4
Female	41	39.8	108	34.3	149	35.6
Family history of PD						
No	87	84.5	259	83.5	346	83.8
Yes	16	15.5	51	16.5	67	16.2
Dyskinesia in hours						
no dyskinesia	0	0.0	315	100.0	315	75.4
< 25% of waking day	70	68.0	0	0.0	70	16.7
>26 of waking day	33	32.0	0	0.0	33	7.9
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Years of education	14.2	4.2	14.0	4.7	14.1	4.5
PD duration at time of measuring dyskinesia	6.2	2.3	5.3	2.1	5.5	2.1
Levodopa equivalent daily dosage	739.3	488.9	601.4	340.4	635.4	386.3
Age of diagnosis PD	64.1	10.9	67.6	10.0	66.7	10.3

	Dyskinesia		No Dyskinesia		Total sample population	
	Total N	N=103 %	Total N	N=315 %	Total N	N=418 %
UPDRS score	26.7	9.9	24.0	12.0	24.7	11.6

N: number. %: percentage. SD: Standard deviation

Table 2

Poisson regression analyses for the association between dyskinesia and the haplotypes for the *DRD1*, *DRD2*, *DRD3* and the *BDNF* loci in PD patients (N=418 patients) with a minimum of 3 years PD disease duration.

	N	Crude	Adj		
	Dysk / No Dysk	**RR**	**RR**	**95%CI**	**p-value**
DRD1 (rs4867798|rs5326|rs265981)					
TCA	67 / 212	Ref			
TCG	64 / 211	0.97	1.00	0.75 – 1.34	0.98
CCG	34 / 109	1.01	1.06	0.74 – 1.52	0.75
CTG	30 / 87	1.07	1.14	0.78 – 1.66	0.50
***DRD2*, block 1** (rs10891549|rs1554929|rs1124493|rs2242592|rs2245805)					
CTAGG	78 / 293	Ref			
TCGTT	60 / 183	1.17	1.20	0.90 – 1.60	0.22
TCAGG	48 / 103	1.51	1.50	1.09 – 2.07	0.01
TCGTG	5 / 30	0.68	0.63	0.26 – 1.52	0.30
***DRD2*, block 2** (rs6265| rs11030101|rs1076563|rs1116313|rs2471857|rs2471854)					
CGCG	87 / 328	Ref			
AACG	62 / 183	1.21	1.25	0.94 – 1.65	0.12
AATC	47 / 105	1.48	1.50	1.10 – 2.03	0.01
***DRD2*, block 3** (rs4245146|rs7122454|rs11214611)					
TGA	79 / 287	Ref			
CGA	86 / 215	1.33	1.29	1.00 – 1.66	0.05
CCG	31 / 113	1.00	1.01	0.69 – 1.48	0.95
***DRD3*, block 1** (rs3732790|rs963468|rs324036)					
TGC	91 / 311	Ref			
AAC	73 / 219	1.10	1.08	0.85 – 1.38	0.52
TGG	30 / 75	1.26	1.26	0.90 – 1.74	0.17
***DRD3*, block 3** (rs226082|rs324026)					
TT	116 / 398	Ref			
CC	72 / 194	1.20	1.23	0.97 – 1.56	0.09

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	N	Crude	Adj		
	Dysk / No Dysk	**RR**	**RR**	**95%CI**	**p-value**
TC	8 / 26	1.04	1.08	0.61 – 1.91	0.80
BDNF (rs6265|rs11030101)					
CT	77 / 202	Ref			
CA	55 / 164	0.91	0.94	0.70 – 1.26	0.67
TA	40 / 76	1.25	1.27	0.93 – 1.72	0.13

Dysk / No Dysk: number of Parkinson's patients with dyskinesia / without dyskinesia. Ref: Reference. 95%CI: 95% confidence interval. NA: not available due to small number of subjects in cells. Adj. = adjusted analysis. Adjusted analysis was adjusted for PEG study, gender, disease duration, levodopa equivalent daily dosage, ethnicity, and age at diagnosis.

Table 3

Poisson regression analyses for the association between 'severity of dyskinesia' and the haplotypes for the *DRD1, DRD2, DRD3* and the *BDNF* loci in PD patients (N=418 patients) with a minimum of 3 years PD disease duration.

	N	Crude	Adj		
	No/Mild/ Severe	**RR**	**RR**	**95%CI**	**p-value**
DRD1 (rs4867798 rs5326|rs265981)					
TCA	212/46/21	**Ref**			
TCG	211 / 46/18	**0.95**	**0.97**	0.71 -1.33	**0.85**
CCG	106/19/15	1.11	1.15	0.78-1.70	**0.48**
CTG	87/21/9	**1.06**	1.14	0.77-1.69	**0.52**
***DRD2*, block 1** (rs10891549|rs1554929|rs1124493|rs2242592|rs2245805)					
CTAGG	293 / 55 / 23	**Ref**			
TCGTT	183/44/16	1.15	1.17	0.87-1.57	**0.29**
TCAGG	103/27/21	**1.68**	**1.62**	1.14-2.30	**0.01**
TCGTG	30/2/3	**0.84**	**0.74**	0.28-2.01	**0.56**
***DRD2*, block 2** (rs6265| rs11030101rs1076563|rs1116313|rs2471857|rs2471854)					
CGCG	328 / 60 / 27	**Ref**			
AACG	183/46/16	**1.16**	**1.20**	0.90-1.60	**0.22**
AATC	105/26/21	**1.63**	**1.62**	1.15-2.28	**0.01**
***DRD2*, block 3** (rs4245146|rs7122454|rs11214611)					
TGA	287 / 56 / 23	**Ref**			
CGA	215/57/29	**1.37**	1.33	1.01 -1.74	**0.04**
CCG	113/19/12	**1.07**	**1.08**	0.72-1.63	**0.71**
***DRD3*, block 1** (rs3732790|rs963468|rs324036)					
TGC	311 / 64 / 27	Ref			
AAC	219 / 49 / 24	1.13	1.11	0.86 – 1.43	0.42
TGG	75 / 18 / 12	1.36	1.35	0.95 – 1.92	0.10
***DRD3*, block 3** (rs226082|rs324026)					
TT	398 / 82 / 34	Ref			
CC	194 / 46 / 26	1.26	1.29	1.00 – 1.65	0.05

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	N	Crude	Adj		
	No/Mild/ Severe	**RR**	**RR**	**95%CI**	**p-value**
TC	26 / 4 / 4	1.21	1.26	0.71 – 2.25	0.43
BDNF (rs6265|rs11030101)					
CT	202 / 54 / 23	Ref			
CA	164 / 40 / 15	0.89	0.92	0.68 – 1.25	0.60
TA	76 / 22 / 18	1.40	1.43	1.01 – 2.03	0.04

No/Mild/Severe: Number of Patients with respectively no, mild or severe dyskinesia. N: Number. Ref: Reference. 95%CI: 95% confidence interval. NA: not available due to small number of subjects in cells. Adj. = adjusted analysis. Adjusted analysis was adjusted for PEG study, gender, disease duration, levodopa equivalent daily dosage, ethnicity, and age at diagnosis.

Table 4

Poisson regression analyses with robust error variance and a log link function for the association between the *DRD2* and *DRD3* risk scores and dyskinesia.

Number of Risk Haplotypes	Dyskinesia					Severity of dyskinesia				
		Crude	Adj.				Crude	Adj.		
		RR	RR	95%CI	p-value		RR	RR	95%CI	p-value
***DRD2*, risk score**										
Continuous		1.17	1.16	1.05 – 1.29	0.004		1.20	1.21	1.08 – 1.35	0.001
	N Dysk / No Dysk					**N No/ Mild / Severe**				
0	20 / 103	Ref				103 / 15 / 5	Ref			
1 to 3	61 / 181	1.55	1.54	0.98 – 2.42	0.06	181 / 41 / 20	1.76	1.61	1.00 – 2.60	0.05
4 to 6	17 / 25	2.49	2.53	1.48 – 4.34	0.001	25 / 10 / 7	3.62	2.80	1.58 – 4.93	<0.001
***DRD3*, risk score**										
Continuous		1.16	1.17	0.99 – 1.40	0.07		1.22	1.20	1.00 – 1.45	0.04
	N Dysk / No Dysk					**N No/ Mild / Severe**				
0	30 / 130	Ref				130 / 22 / 8	Ref			
1	62 / 164	1.46	1.45	0.99 – 2.12	0.06	164 / 40 / 22	1.57	1.53	1.02 – 2.30	0.04
2 to 4	6 / 15	1.52	1.72	0.78 – 3.81	0.18	15 / 4 / 2	1.60	1.84	0.79 – 4.31	0.16

N Dysk / No Dysk: number of Parkinson's patients with dyskinesia / without dyskinesia. No/Mild/Severe: Number of Patients with respectively no, mild or severe dyskinesia. Ref: Reference category. 95%CI: 95% confidence interval. Adj. = adjusted analysis. Adjusted analysis was adjusted for PEG study, gender, disease duration, levodopa equivalent daily dosage, ethnicity, and age at diagnosis.