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Role of LINGO1 polymorphisms in Parkinson's disease

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Abstract

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A clinical overlap between Parkinson's disease (PD) and essential tremor (ET) has prompted a discussion whether these conditions share common genetic susceptibility factors. Recently, the first genome-wide association study in ET revealed a significant association with a variant in the LINGO1 gene. LINGO1 has also been demonstrated to play a role in the survival of dopaminergic neurons in an animal model of PD, and therefore constitutes a potential candidate gene for PD. In this present study, SNPs rs9652490, rs11856808, rs7177008 of LINGO1 were genotyped in a total of 694 Austrian subjects (349 PD, 345 controls). No association could be found between genotype or allele counts and PD. Neither did a subgroup analysis in tremor-dominant PD patients reveal a significant association. This study on LINGO1-variants in PD argues against a major role of LINGO1 gene variations for PD.

Keywords

Essential Tremor; Parkinson's disease; LINGO1; genetics; association study

Introduction

The identification of genetic variants associated with PD does not only contribute to the research on the etiology of the disease in certain populations, but also provides further insight into potential pathophysiological mechanisms in PD. However, monogenic forms of PD do not explain the etiology of the vast majority of patients with an apparently sporadic, so called "classic", late-onset disease. A significant overlap between the diagnoses of PD and ET is frequently observed. In retrospective analyses, 6–20% of ET patients have been described to also exhibit signs of parkinsonism.^{1, 2} A recent prospective study demonstrated that patients with ET have a four-fold elevated risk to develop PD over an observational period of 3.3 years.³ Conversely, a diagnosis of ET was proposed to be 5 to 10 times more likely in subjects with PD than in controls.⁴ Furthermore, it has been demonstrated that the risk of ET in first-degree relatives of PD patients is significantly elevated.⁵ A neuropathological study demonstrated the occurrence of Lewy bodies in the brainstem in an older subset of ET patients.⁶ However, these findings were not confirmed by others.⁷ Although not all available studies confirm an association between ET and PD,⁸ recently published prospective data suggest potential susceptibility factors that might be shared between ET and PD.

Despite the high heritability of ET, the quest for a causative genetic background has not revealed unequivocally associated genes so far. Recently, the first genome-wide association study in ET demonstrated a significant association with a sequence variant of the LINGO1 gene, exhibiting a population-attributable risk of 20%.⁹

LINGO1 (Leucine-rich repeat and Ig domain-containing Nogo receptor interacting protein 1, OMIM #609791), located at 15q24, codes for a transmembrane adhesion and cell-cell interaction protein and is exclusively expressed in the central nervous system. LINGO1 has been demonstrated to negatively regulate axonal outgrowth and plays a role in early brain development and oligodendrocyte differentiation.¹⁰ Due to its presumed role in neuronal survival and myelination, LINGO1 has been targeted in vivo and in vitro in models of spinal cord injury, autoimmune encephalitis and PD. In a study using the 6-OHDA model, selective inhibition of LINGO1 promoted survival of dopaminergic neurons as well as neuronal outgrowth.¹¹

The aim of this present study was therefore to characterize whether LINGO1 sequence variants are associated with PD in a sample of Austrian PD patients. We furthermore examined whether genetic variants in LINGO1 are associated with tremor-dominant PD.

Tremor-dominant PD, or benign tremulous PD, is thought to exhibit a more benign disease course and a higher rate of familial occurrence. This suggests a potentially enhanced genetic influence in this subtype of PD.¹²

Study population and methods

After obtaining written informed consent, 9 ml peripheral venous blood was drawn from 349 subjects (101 female) diagnosed with idiopathic PD according to standard clinical criteria (UK Brain Bank). Clinical diagnosis was made by a neurologist specialized in movement disorders. Atypical or secondary parkinsonian syndromes were excluded. In 233 patients, information on motor-subtypes was available. A subset of 34 patients (16 female) fulfilled the criteria of tremor-dominant PD,¹² as opposed to 199 patients with a motor subtype of either predominant bradykinesia/rigidity or an intermediate phenotype. 21.5% (n=75) of the total patient sample reported at least one first or second degree relative with PD. The relatively high proportion of positive family history in our sample could be explained by a selection bias of a tertiary, university-based referral center. At time of the examination, mean age in the patient group was 69.4±9.8 years. Mean age of PD onset was 59.5±14.1 years. 345 control subjects (140 female) were recruited as volunteers without known history of neurological disease through the outpatient clinic of the Department of Neurology, Medical University of Vienna e.g. as accompanying unrelated spouses or blood donors. Control subjects and patients shared the same middle-European ethnic background. Median age of controls at the time of the study was 41 years. The gender distribution between cases and controls was significantly different (chi-square-test: $p<0.005$). Clinical phenotyping, DNA collection as well as genetic analyses were performed under a protocol approved by the ethics committee of the Medical University of Vienna.

After collection of blood, DNA was extracted and amplified using standard procedures and genotyping was performed via commercially available Taq Man-based allelic discrimination assays (Applied Biosystems®). The following SNPs of LINGO1 were genotyped: rs9652490, rs11856808, rs7177008. Target-SNPs were chosen based on the following observations: Allele G of SNP rs9652490 has been shown to be genome-wide significantly associated with ET; the neighboring SNPs rs11856808 (T) and rs7177008 (G) also showed suggestive association, but this did not reach genome-wide significance.⁹

For the assessment of allelic and genotypic differences between cases and population controls, standard Pearson's chi-square statistics and the Armitage's trend test as implemented in the web-based statistics utility of the Institute for Human Genetics, Munich, Germany, were used (<http://ihg2.helmholtz-muenchen.de/>). For evaluation of concordance with Hardy-Weinberg-Equilibrium in cases and controls, the Exact test was calculated.

For subgroup analyses patients with tremor-dominant PD (TDP) were compared with other PD-subtypes combined (Non-TDP). The level of statistical significance was defined as $p<0.05$.

Results

Our data show that genotypes and alleles were equally distributed between PD patients and controls for the analyzed SNPs rs9652490, rs11856808, and rs7177008. In particular, we found no association between the G allele of rs9652490-SNP and PD, which previously has been reported to be associated with ET (see table 1). In the subgroup of patients with tremor-dominant PD, no significant differences of allele or genotype frequencies were observed for any of the three SNPs in comparison to patients with a non-tremor-dominant motor subtype (see table 1). Furthermore, a secondary analysis based on family history of PD revealed no

significant differences in genotype or allele counts between familial and sporadic PD (*data not shown*).

Discussion

It is a well-established observation, described in independent populations and in a prospective manner that the risk for incident PD in patients already affected by ET – and vice versa – is significantly higher than in the general population.^{3, 4} A shared genetic susceptibility factor has been postulated to explain the co-occurrence of PD and ET within families and individuals. In an Italian family affected by both disease entities with pseudo-dominant inheritance, a *parkin* mutation was detected as genetic correlate.¹³ However, no genes have so far been described to confer to the risk of both disease entities on a larger sample. While several genetic predisposing factors have been described in PD, analyses of the *parkin* and *LRRK2* genes have not shown associations in ET cohorts.^{14, 15} This study investigated variants in *LINGO1*, a recently described risk-gene for ET, in a sample of PD-patients from Austria. However, no association could be demonstrated between *LINGO1*-genotype or allele-count and PD in our sample. Furthermore, *LINGO1*-variants do not seem to play a relevant role in subjects with tremor-dominant PD. However, as the subgroup of tremor-dominant PD cases was rather small with 34 cases, a small effect cannot be excluded at this stage. More such cases would be necessary to draw a valid conclusion.

Allele G of rs9652490 has been shown to be associated with ET with an odds ratio (OR) of 1.55 in the total sample, and an OR of 1.73 in an Austrian replication sample.⁹ Our present study on 349 cases and 345 controls from Austria could not demonstrate a significant association of SNP rs9652490 with PD. However, we cannot exclude a weak association signal that might be detected in larger sample sizes.

The main methodological limitation of the present study is the fact that cases and controls were not age-matched. However, we think that this does not diminish the conclusion of our study. As the prevalence of PD can be estimated to be about 1% at the age of 60 years, we would roughly expect 3 to 4 individuals from the control group to develop the disease by this age. Irrespective of the assumed genotypes of these potentially presymptomatic cases, no difference in the overall statistical result would be expected. Thus, since the observed genotype and allele-frequencies are largely equally distributed, no post-hoc correction for age effects was performed.

Although not reaching statistical significance in the genotype association tests, genotype GG or rs9652490 was more frequent in cases than in controls (6.0 vs. 3.8%). This might explain the departure from the Hardy-Weinberg Equilibrium (HWE) in the group of cases (Exact test: $p=0.02$). A possible correlate for the HWE departure could be a weak association, which was not discovered using the association models calculated in the present study. However, a post-hoc analysis assuming a recessive model did not reveal a significant association (risk allele G, $p=0.48$). A genotyping error as explanation for HWE departure is unlikely since rs7177008, a SNP in strong linkage disequilibrium to rs9652490, shows identical genotype distributions and also exhibits the departure. Another explanation of departure of HWE could be the presence of deletions or duplications in the genomic region of the SNP, which is located in intron 3 of *LINGO1*. According to the publicly available database on copy number variations (<http://projects.tcag.ca/variation/>), no common deletions or duplications are described in the genomic region spanning 50kb surrounding rs9652490. These findings warrant future studies including sequencing of the genomic region of *LINGO1* in cases and controls, as well as studies on larger sample sizes.

To summarize, this present study could not detect an effect of LINGO1 variants, which have been demonstrated to be associated with ET, neither on PD nor on a subgroup of patients with tremor-dominant PD. LINGO1 represents a potential candidate gene in PD because of its regulatory role in the survival of dopaminergic neurons in the 6-OHDA model. In conclusion, the SNPs of the gene LINGO1, which were implicated in association with ET, do not seem to be a strong risk factor or functional variant for PD in this Austrian population. However, we cannot rule out whether other LINGO1 variants influence the risk for PD.

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Role of the authors

D. Haubenberger: conception of the project, collection of data and samples, data collection and analysis, writing of the first manuscript draft

Christoph Hotzy: processing of DNA samples and genotyping, critical appraisal of the manuscript

W. Pirker: collection of data and samples, critical appraisal of the manuscript

R. Katzenschlager: collection of data and samples, critical appraisal of the manuscript

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E. Auff: collection of data and samples, critical appraisal of the manuscript

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Genotype and allelic distribution of candidate SNPs rs9652490, rs11856808, rs7177008 between all PD patients (n=349) and controls (n=345), as well as tremor-dominant PD patients (TDP, n=34) and non-tremor-dominant PD patients (Non-TDP, n=199).

Table 1

SNP	Genotype / Allele	Patients, n (%)	Controls, n (%)	p-values ¹	TDP patients, n (%)	Non-TDP patients, n (%)	p-values ¹
rs9652490*	A/A	230 (66.1)	223 (65.2)		21 (61.8)	135 (68.2)	
	A/G	97 (27.9)	106 (31.0)		11 (32.4)	50 (25.3)	
	G/G	21 (6.0)	13 (3.8)	0.76	2 (5.9)	13 (6.6)	0.61
	A	557 (80.0)	552 (80.7)		53 (77.9)	320 (80.8)	
	G	139 (20.0)	132 (19.3)	0.75	15 (22.1)	76 (19.2)	0.58
rs11856808	C/C	156 (44.7)	155 (45.5)		15 (44.1)	94 (47.2)	
	C/T	150 (43.0)	144 (42.2)		13 (38.2)	82 (41.2)	
	T/T	43 (12.3)	42 (12.3)	0.88	6 (17.6)	23 (11.6)	0.47
	C	462 (66.2)	454 (66.6)		43 (63.2)	270 (67.8)	
	T	236 (33.8)	228 (33.4)	0.88	25 (36.8)	128 (32.2)	0.45
rs7177008*	C/C	231 (66.2)	217 (64.8)		21 (61.8)	136 (68.3)	
	C/G	97 (27.8)	106 (31.6)		11 (32.4)	50 (25.1)	
	G/G	21 (6.0)	12 (3.6)	0.82	2 (5.9)	13 (6.5)	0.60
	C	559 (80.1)	540 (80.6)		53 (77.9)	322 (80.9)	
	G	139 (19.9)	130 (19.4)	0.81	15 (22.1)	76 (19.1)	0.57

¹ Armitage's trend test for genotype comparisons and Pearson's goodness-of-fit chi-square-test for allele comparisons (all p-values are shown without correction for multiple testing)

* Cases showed a significant departure from Hardy-Weinberg equilibrium.