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LINGO1 rs9652490 is associated with Essential Tremor and Parkinson Disease

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Abstract

Recently, a variant in *LINGO1* (rs9652490) was found to associate with increased risk of essential tremor. We set out to replicate this association in an independent case-control series of essential tremor from North America. In addition, given the clinical and pathological overlap between essential tremor and Parkinson disease, we also evaluate the effect of *LINGO1* rs9652490 in two case-control series of Parkinson disease. Our study demonstrates a significant association between *LINGO1* rs9652490 and essential tremor (*P*=0.014) and Parkinson disease (*P*=0.0003), thus providing the first evidence of a genetic link between both diseases.

Keywords

LINGO1; Parkinson disease; essential tremor

Introduction

A single genetic variation within the leucine-rich repeat and Ig domain containing 1 (*LINGO1*) locus was recently found to be associated with an increased risk of essential tremor (ET) [1]. Although ET is the most common movement disorder with a high degree of inheritance, genetic factors have remained elusive. Three loci have been identified in multi-incident kindreds with familial ET for which candidate genes have been nominated, but none reproducibly [2]. Stefansson and colleagues performed a genome-wide association study on

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452 ET patients and almost 15,000 controls from Iceland, nominating SNP rs9652490 located within *LINGO1* as a risk allele (*P*-value = 3.0×10^{-7}). Follow-up in a number of ET patient-control series from Europe and the US provided further support (combined *P*-value = 1.2×10^{-9}) [1]. Nevertheless, with all novel genetic associations the best evidence comes from replication by independent groups, therefore we set out to examine this variant in a North American ET patient-control series. In addition, given the clinical overlap of ET with another common movement disorder, Parkinson disease (PD), we expanded our study to include two PD patient-control series from the US and Europe.

Methods

We included 356 ET patients from North America with a mean age of 70.9 ± 13.3 years (age at onset 52.8 ± 19.1 years). The PD cases series consisted of 426 patients from North America with a mean age of 72.2 ± 11.0 years (age at onset 61.9 ± 12.2) and 618 patients from Norway with a mean age of 72.7 ± 10.7 years (age at onset 59.0 ± 11.2). The control groups consisted of unrelated individuals and spouses, and included 428 subjects from North America (mean age 72.2 ± 10.8 years) and 602 from Norway (mean age 70.5 ± 12.3 years); they were all free of known neurological disease. Detailed information for each series is given in table 1. All samples were of Caucasian descent, and all patients were examined and observed longitudinally by a movement disorder neurologist (Z.K.W., R.J.U., J.O.A. or A.R.) and diagnosed according to standard criteria. ET patients satisfied clinical criteria for definite or probable ET [3,4]. The ethical review board of each institution approved the study and all participants provided informed consent. Genotyping for all groups was consistent with Hardy-Weinberg equilibrium (*P*>0.05). Genotyping was performed using a TaqMan probe on an ABI7900. Individual genotypic associations were investigated by chi-square test.

Results

The analysis of our ET patient-control series from North America indicated a significant association between the *LINGO1* rs9652490 A allele and risk of disease (*P*=0.014; OR=2.2) (Table 2). To evaluate the role of this variant in PD, we additionally genotyped 426 PD patients from North America. Similar to the results obtained for ET, there was evidence of a significant association between *LINGO1* and an increased risk of PD (*P*=0.012; OR=2.1). The association was again driven by those samples carrying allele A of rs9652490 (Table 2). To further confirm the association with PD we genotyped an independent case-control series from Norway consisting of 618 PD cases and 602 control subjects. This analysis showed an increased frequency of the rs9652490 A allele in PD cases compared to control subjects (*P*=0.008; OR=1.7). The combined PD series (US and Norway) resulted in a highly significant association ($P=3.4\text{x}10^{-4}$) and a 1.8-fold increased disease risk. Combining all cases (PD and ET) we obtained a similar 1.9-fold increased risk of disease ($P=1.3\text{x}10^{-4}$). Statistical analysis for allelic association is provided as a supplemental table. Significant differences were not observed between familial and sporadic cases, male and female patients or those with age of disease onset above or below the median (*P*>0.05).

Discussion

Herein we show an association between SNP rs9652490 in *LINGO1* and ET, and that the same allele is associated with PD. Prior evidence for a common link between ET and PD comes from clinical, epidemiological and pathological studies suggesting: (1) a four-fold increased risk of PD in patients with ET; (2) increased prevalence of ET in relatives of patients with PD, (3) the presence of action tremor preceding the onset of PD symptoms indicating ET as an early manifestation of PD, and (4) the presence of brainstem Lewy bodies at autopsy in patients with ET [5–7]. A caveat of clinical and epidemiological studies is the observational bias of both

family members and movement disorder neurologists. The type and origin of tremor in ET (with activation) and PD (at rest) have usually been considered etiologically distinct.

The association in our study and that previously described by Stefansson *et al.* appear to be driven by different alleles, although the original paper does not provide genotype distributions making a detailed comparison of genotypic results difficult. Given that SNP rs9652490 is most likely not the functional variant but in linkage disequilibrium with a nearby functional locus there is a plausible explanation. The study of isolated populations such as in the case of Iceland can lead to the identification of common populationspecific risk variants as previously observed in PD [8]. This phenomenon may explain the association with alternate alleles of the same SNP tagging different functional variants or the same variant on a different ancestral haplotype. These observations could also be a chance event, which warrants further study of *LINGO1* variants including rs9652490 in other population samples. It may be insightful to examine the specificity of this finding in other neurodegenerative diseases and demyelinating disorders.

In the original report, only one of the populations used to replicate the finding was significant; this may be explained by the small number of samples used for the replication of their genome-wide association (GWA) data in ET [1]. Similarly, GWA studies in PD have not previously nominated *LINGO1* as a susceptibility locus. The first reported GWA of PD did not examine SNP rs9652490, nevertheless four neighboring SNPs located within *LINGO1* were not significantly associated with disease [9]. Two other GWA studies examined SNP rs9652490 and also failed to identify an association with PD [10,11]. Whether this is due to limited power, uncertainty in the clinical diagnosis of PD in patients and control subjects, or simply the background genetic heterogeneity of the North American samples employed is presently unclear. One potential caveat of our study is ascertainment inaccuracy given that misdiagnosis may occur in as many as 37 percent of ET patients and in 10–20 percent of PD patients [12–13]. One study found that the majority of patients misdiagnosed as ET in fact have PD, which may be a confounding factor in our study. More specifically, it is conceivable that the ET group in our study contains a significant number of patients with PD, thereby participating in the association observed in both PD and ET groups. However, given the similar sample sizes, *P*-values and odds ratios obtained in the PD and the ET groups, it is unlikely that the association is driven only by PD patients in both groups. Therefore, based on our observations, further studies and meta-analyses are warranted to test the association of *LINGO1* rs9652490 with ET and PD, and to identify the functional variant responsible for disease risk.

The genetic association of the *LINGO1* locus with both ET and PD susceptibility is supported by the functional role of its encoded protein. LINGO1 is a central nervous system-specific protein component of the Nogo-66 receptor (NgR1)/p75/LINGO1 signaling complex implicated in inhibition of oligodendrocyte differentiation, axonal myelination and regeneration, and neuronal survival [14–19]. Expression of *LINGO1* is increased after neuronal damage or cell death, and its inhibition promotes functional recovery and axonal sprouting after spinal cord injury [15,16,20]. The expression of *LINGO1* is elevated in the *substantia nigra* of patients with PD compared to age-matched controls, and in ventral midbrain neurons in animal models of PD after neurotoxic lesions [20]. Furthermore, reduction of LINGO1 activity has been shown to improve survival, growth and function of dopaminergic neurons both in primary cell cultures and *in vivo* experimental models of parkinsonism in rodents [20]. The association of both ET and PD with *LINGO1* provides the first genetic evidence that the pathophysiology of these common movement disorders may be connected.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, Jonsdottir GA, et al. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet 2009;41(3):277–279. [PubMed: 19182806]
2. Deng H, Le W, Jankovic J. Genetics of essential tremor. Brain 2007;130(Pt 6):1456–1464. [PubMed: 17353225]
3. Louis ED, Ford B, Lee H, Andrews H, Cameron G. Diagnostic criteria for essential tremor: a population perspective. Arch Neurol 1998;55(6):823–828. [PubMed: 9626774]
4. Uitti RJ, Baba Y, Wszolek ZK, Putzke DJ. Defining the Parkinson's disease phenotype: initial symptoms and baseline characteristics in a clinical cohort. Parkinsonism Relat Disord 2005;11(3): 139–145. [PubMed: 15823477]
5. Shahed J, Jankovic J. Exploring the relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord 2007;13(2):67–76. [PubMed: 16887374]
6. Barbeau A, Pourcher E. New data on the genetics of Parkinson's disease. Can J Neurol Sci 1982;9(1): 53–60. [PubMed: 7093827]
7. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007;130(Pt 12):3297–3307. [PubMed: 18025031]
8. Ross OA, Wu YR, Lee MC, Funayama M, Chen ML, Soto AI, et al. Analysis of Lrrk2 R1628P as a risk factor for Parkinson's disease. Ann Neurol 2008;64(1):88–92. [PubMed: 18412265]
9. Maraganore DM, de Andrade M, Lesnick TG, Strain KJ, Farrer MJ, Rocca WA, et al. High-resolution whole-genome association study of Parkinson disease. Am J Hum Genet 2005;77(5):685–693. [PubMed: 16252231]
10. Fung HC, Scholz S, Matarin M, Simon-Sanchez J, Hernandez D, Britton A, et al. Genome-wide genotyping in Parkinson's disease and neurologically normal controls: first stage analysis and public release of data. Lancet Neurol 2006;5(11):911–916. [PubMed: 17052657]
11. Pankratz N, Wilk JB, Latourelle JC, DeStefano AL, Halter C, Pugh EW, et al. Genomewide association study for susceptibility genes contributing to familial Parkinson disease. Hum Genet 2009;124(6):593–605. [PubMed: 18985386]
12. Jain S, Lo SE, Louis ED. Common misdiagnosis of a common neurological disorder: how are we misdiagnosing essential tremor? Arch Neurol 2006;63(8):1100–1104. [PubMed: 16908735]
13. Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease. Neurology 2001;57(8):1497–1499. [PubMed: 11673599]
14. Carim-Todd L, Escarceller M, Estivill X, Sumoy L. LRRN6A/LERN1 (leucine-rich repeat neuronal protein 1), a novel gene with enriched expression in limbic system and neocortex. Eur J Neurosci 2003;18(12):3167–3182. [PubMed: 14686891]
15. Ji B, Li M, Wu WT, Yick LW, Lee X, Shao Z, et al. LINGO-1 antagonist promotes functional recovery and axonal sprouting after spinal cord injury. Mol Cell Neurosci 2006;33(3):311–320. [PubMed: 17011208]
16. Mi S, Hu B, Hahm K, Luo Y, Kam Hui ES, Yuan Q, et al. LINGO-1 antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomyelitis. Nat Med 2007;13(10):1228–1233. [PubMed: 17906634]
17. Mi S, Lee X, Shao Z, Thill G, Ji B, Relton J, et al. LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci 2004;7(3):221–228. [PubMed: 14966521]
18. Mi S, Miller RH, Lee X, Scott ML, Shulag-Morskaya S, Shao Z, et al. LINGO-1 negatively regulates myelination by oligodendrocytes. Nat Neurosci 2005;8(6):745–751. [PubMed: 15895088]

19. Shao Z, Browning JL, Lee X, Scott ML, Shulga-Morskaya S, Allaire N, et al. TAJ/TROY, an orphan TNF receptor family member, binds Nogo-66 receptor 1 and regulates axonal regeneration. Neuron 2005;45(3):353–359. [PubMed: 15694322]

20. Inoue H, Lin L, Lee X, Shao Z, Mendes S, Snodgrass-Belt P, et al. Inhibition of the leucine-rich repeat protein LINGO-1 enhances survival, structure, and function of dopaminergic neurons in Parkinson's disease models. Proc Natl Acad Sci U S A 2007;104(36):14430–14435. [PubMed: 17726113]

Table 1

Sample demographics for the series analyzed.

	Group	n	Age (years) mean ± SD	AOO mean ± SD	Gender ratio (Male:Female)	Samples with family history of disease
North America						
US	Control	428	72.2 ± 10.8	NA	1:0.91	NA
	PD	426	72.2 ± 11.0	61.9 ± 12.2	1:0.81	149 (20*)
	ET	150	72.3 ± 13.0	50.9 ±19.7	1:0.97	100 (34#)
Canada	ET	203	70.0 ± 13.5	54.7 ± 18.1	1:1.67	53 (12#)
Norway	Control	602	70.5 ± 12.3	NA	1:0.85	NA
	PD	618	72.7 ± 10.7	59.0 ± 11.2	1:0.76	NR

Disease was considered familial if at least one 1st to 3rd degree relative was affected; subset of patients with family history of additional neurological diseases are given in brackets (*ET or dystonia; #PD or dystonia); AOO, age of onset; NA, not applicable; NR, not reported.

Table 2

Frequency and statistical analysis of *LINGO1* rs9652490 in Parkinson disease and essential tremor series. Sample sizes given for each genotype account for genotyping failure.

Discovery	**North America**									
rs9652490	**Controls**		**PD**				**ET**			
Genotype	**n**	**freq**	**n**	**freq**	**P-value**	**OR (95%CI)**	**n**	**freq**	**P-value**	**OR (95%CI)**
A/A	229	0.574	238	0.579	**0.0117**	**2.1 (1.1–3.8)**	215	0.609	**0.0145**	**2.2 (1.1–4.2)**
A/G	137	0.343	156	0.380			124	0.351		
G/G	33	0.083	17	0.041			14	0.040		
Replication	**Norway**									
rs9652490	**Controls**		**PD**							
Genotype	**n**	**freq**	**n**	**freq**	**P-value**	**OR (95%CI)**				
A/A	332	0.575	318	0.547	**0.0078**	**1.7 (1.0–2.7)**				
A/G	200	0.347	235	0.404						
G/G	45	0.078	28	0.048						
Meta-analysis										
rs9652490	**Controls**		**Combined PD**				**Combined PD and ET**			
Genotype	**n**	**freq**	**n**	**freq**	**P-value**	**OR (95%CI)**	**n**	**freq**	**P-value**	**OR (95%CI)**
A/A	561	0.575	556	0.560	**$3.4x10^{-4}$**	**1.8 (1.3–2.7)**	771	0.573	**$1.3x10^{-4}$**	**1.9 (1.3–2.7)**
A/G	337	0.345	391	0.394			515	0.383		
G/G	78	0.080	45	0.045			59	0.044		