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LINGO1 and risk for essential tremor: Results of a meta-analysis of rs9652490 and rs11856808

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ABSTRACT

Background/objectives: Recently, a genome-wide association study revealed a significant statistical association between *LINGO1* rs9652490 and rs11856808 polymorphisms and the risk of developing essential tremor (ET) in Icelandic people. Because the results of further association studies were controversial, we conducted a meta-analysis including all the studies published on the risk of ET related with these polymorphisms.
Methods: The metaanalysis included 11 association studies between *LINGO1* rs9652490 (3972 ET patients, 20,714 controls) and 7 association studies between *LINGO1* rs11856808, and risk for ET (2076 ET patients, 18,792 controls), and was carried out by using the software *Meta-Disc 1.1.1* (http://www.hrc.es/investigacion/metadisc.html; Unit of Clinical Statistics, Hospital Ramón y Cajal, Madrid, Spain). Heterogeneity between studies in terms of degree of association was tested using the Q-statistic.
Results: Global diagnostic odds-ratios (ORs) and 95% confidence intervals (CI) for rs9652490 and rs11856808 of the total series were, respectively, 1.17 (1.00–1.36) ($p = 0.069$) and 1.20 (1.05–1.36) ($p = 0.016$). After excluding data on Icelandic people of the discovery series (that was responsible of a high degree of heterogeneity for rs9652490 polymorphism), the ORs and CI were 1.10 (0.97–1.26) ($p = 0.063$) and 1.12 (0.99–1.27) ($p = 0.034$). Global ORs and 95% CI for rs9652490 and rs11856808 of familial ET patients were, respectively, 1.27 (1.03–1.57) ($p = 0.014$) and 1.21 (1.10–1.44) ($p = 0.031$).
Conclusions: The results of the meta-analysis suggest a relationship between *LINGO1* rs11856808 polymorphism and the risk for ET and for familial ET, while rs9652490 polymorphism was only related with the risk for familial ET.

1. Introduction

Essential tremor (ET) is characterized by postural or kinetic 4–12 Hz tremor involving mainly the hands and forearms, although it can also be extended to the head, chin, voice, and other body parts. Family history of tremor among subjects with ET ranges from 17.4% to 100%, and is significantly more frequent than in controls. Linkage studies identified three susceptibility loci for ET at chromosomes 3q13, 2p24.1, and 6p23 [1].

LINGO1 (leucine rich repeat and Ig domain containing Nogo receptor interacting protein-1) is a transmembrane protein expressed in neural cells, which inhibits the differentiation of oligodendrocyte precursor cells into mature oligodendrocytes, as well as myelination and remyelination processes [2,3]. *LINGO1* comprises 12 leucine rich repeats followed by an immunoglobulin (Ig) domain and a short cytoplasmic tail, and is encoded by the *LINGO1* gene (OMIM 609791) located in the chromosome 15q24.3 [4,5]. On neurons, *LINGO1* simultaneously interacts with the Nogo-66 receptor (NgR) and $p75^{NTR}$ or TROY to form a receptor complex that binds the associated glycoprotein and oligodendrocyte myelin glycoprotein resulting in the restriction of axonal elongation via activation of the small GTPase RhoA [5–7]. *LINGO1* expression is elevated in the substantia nigra of Parkinson's disease (PD) subjects compared with controls, and dopaminergic neurons of *LINGO1* knockout mice are protected against degeneration [8]. *LINGO1* shares structural properties with Leucine-Rich Repeat Kinase 2 gene (LRRK2; OMIM ref*609007), which has been linked

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to familial PD [9,10]. Thus, *LINGO1* is an interesting candidate to modify risk of familial ET.

Recently, a genome-wide association study (GWAS) by Stephansson et al. [11], revealed a significant statistical association between *LINGO1* rs9652490 and rs11856808 polymorphisms and the risk of ET in Icelandic people. Since then, 5 studies found association between rs9652490 polymorphism and ET [12–16], while other 5 studies failed to confirm this association [17–21]. Regarding rs11856808 polymorphism and risk for ET, Thier et al. [14] confirmed the association, while other 5 groups found absence of association [16,17,19–21].

In an attempt to provide an answer to these controversial results, a meta-analysis of all available studies relating the *LINGO1* rs9652490 and rs11856808 polymorphisms to the risk of developing ET was conducted. In the meta-analysis both, estimates of the genetic association of each individual study and a pooled estimate of this association were obtained. In addition, the heterogeneity between studies and publication bias were investigated. The *LINGO1* rs9652490 and rs11856808 polymorphisms were analyzed separately.

2. Material and methods

All studies that investigated the association of the *LINGO1* rs9652490 and rs11856808 polymorphisms with the development of ET and published before October 15, 2011 were considered in the meta-analysis. The studies were identified by extended computer-based searches of the PubMed database. From each study, the following information was extracted: first author, journal, year of publication, demographics, matching, validity of genotyping method, and the number of cases and controls for each *LINGO1* rs9652490A/G and rs11856808C/T genotypes. Allele frequencies were calculated, for cases and controls, from the available genotype distributions.

Due to possible statistical inconsistencies and design differentiations between the studies, the significance of the association between the alleles of *LINGO1* rs9652490 (A and G alleles), *LINGO1* rs11856808 (C and T alleles) as well as the risk of having ET was tested for each study. All associations were indicated as diagnostic odds ratios (OR) with the corresponding 95% confidence interval (CI). Based on individual ORs, fixed effects of the pooled OR and random pooled OR effects were estimated. Meta-analysis of case–control studies was carried out by using the software *Meta-DiSc 1.1.1* (http://www.hrc.es/investigacion/metadisc.html; Unit of Clinical Statistics, Hospital Ramón y Cajal, Madrid, Spain) [22]. The global diagnostic OR was calculated with the Mantel–Haenszel method [23] when no heterogeneity was observed. If statistically significant heterogeneity existed, then the global diagnostic OR was calculated with the DerSimonian–Laird method [24].

Heterogeneity between studies in terms of degree of association was tested using the Q-statistic, which is a weighted sum of squares of the deviations of individual study OR estimates from the overall estimate [25]. When ORs are homogeneous, Q follows a chi-squared distribution with r-1 (r is the number of studies) degrees of freedom (d.f.). If $p<0.10$, then heterogeneity was considered significant. Heterogeneity was quantified with the I^2 metric ($I^2 = (Q)d.f.)/Q$), which is independent of the number of studies in the meta-analysis [26]. I^2 takes values between 0% and 100% with higher values denoting greater degree of heterogeneity ($I^2 = 0$–25%: no heterogeneity; $I^2 = 25$–50%: moderate heterogeneity; $I^2 = 50$–75%: large heterogeneity; $I^2 = 75$–100%: extreme heterogeneity).

3. Results

The search using the PubMed database showed a total of 11 studies analyzing the association between the SNP rs9652490 and the risk for ET (3972 ET patients and 20,714 controls) and 7 studies on the association between the rs11856808 SNP and the risk for ET (2076 ET patients and 18,792 controls). Table 1 summarizes data from these studies,

Table 1
Frequency or the allelic variants rs9652490G and rs11856808T in the total series of ET patients and healthy volunteers in different reports with their diagnostic odd-ratios (OR) and 95% confidence intervals (CI).

Allelic variant	Authors (reference)	Country	Total et patients n (frequency)	Controls n (FREQUENCY)	Diagnostic OR (95% CI)	P value
rs 9652490(G)	Stefansson et al. [11]	Iceland (discovery)	452 (0.329)	14,378 (0.230)	1.65 (1.35–2.01)	3.0×10^{-7}
	Stefansson et al. [11]	Austria (follow-up)	77 (0.292)	342 (0.193)	1.67 (0.95–2.94)	0.071
	Stefansson et al. [11]	Germany (follow-up)	69 (0.297)	176 (0.233)	1.34 (0.72–2.51)	0.355
	Stefansson et al. [11]	U.S.A. (follow-up)	119 (0.273)	611 (0.222)	1.28 (0.82–2.01)	0.272
	Stefansson et al. [11]	Iceland (follow-up)	35 (0.271)	290 (0.224)	1.20 (0.53–2.68)	0.661
	Tan et al. [12]	Singapore	190 (0.263)	734 (0.218)	1.27 (0.88–1.84)	0.200
	Vilariño-Güell et al. [13]	U.S.A., Canada	353 (0.215)	399 (0.254)	0.81 (0.58–1.14)	0.223
	Thier et al. [14]	Germany	284 (0.240)	334 (0.160)	1.67 (1.12–2.49)	0.012
	Thier et al. [14]	France	48 (0.260)	240 (0.170)	1.62 (0.78–3.37)	0.197
	Vilariño-Güell et al. [15]	U.S.A., Canada	1236 (0.215)	629 (0.239)	0.88 (0.70–1.10)	0.254
	Clark et al. [16]	U.S.A.	257 (0.242)	265 (0.193)	1.33 (0.88–2.03)	0.176
	Zuo et al. [17]	China	109 (0.212)	430 (0.216)	0.97 (0.58–1.62)	0.905
	Wu et al. [18]	China	117 (0.252)	160 (0.259)	0.96 (0.55–1.66)	0.894
	Lorenzo-Betancor et al. [19]	Spain	226 (0.152)	1117 (0.171)	0.86 (0.58–1.28)	0.451
	Bourassa et al. [20]	France, Canada	259 (0.220)	479 (0.220)	1.01 (0.70–1.45)	0.978
	Radovica et al. [21]	Latvia	141 (0.199)	130 (0.196)	1.04 (0.57–1.90)	0.897
	Total group		3972 (0.237)	20,714 (0.223)	1.17 (1.00–1.36)	0.069
	Total group excluding Iceland discovery series		3520 (0.225)	6336 (0.209)	1.10 (0.97–1.26)	0.063
rs11856808(T)	Stefansson et al. [11]	Iceland (discovery)	452 (0.451)	14,378 (0.352)	1.51 (1.25–1.83)	3.0×10^{-6}
	Stefansson et al. [11]	Austria (follow-up)	77 (0.422)	342 (0.334)	1.42 (0.86–2.36)	0.172
	Stefansson et al. [11]	Germany (follow-up)	69 (0.370)	176 (0.335)	1.20 (0.67–2.14)	0.539
	Stefansson et al. [11]	U.S.A. (follow-up)	119 (0.371)	611 (0.358)	1.05 (0.70–1.58)	0.814
	Stefansson et al. [11]	Iceland (follow-up)	35 (0.400)	290 (0.314)	1.46 (0.71–3.00)	0.304
	Thier et al. [14]	Germany	284 (0.330)	334 (0.280)	1.26 (0.90–1.78)	0.182
	Thier et al. [14]	France	48 (0.420)	240 (0.300)	1.67 (0.88–3.15)	0.114
	Clark et al. [16]	U.S.A.	257 (0.406)	265 (0.367)	1.18 (0.83–1.68)	0.365
	Zuo et al. [17]	China	109 (0.335)	430 (0.332)	1.03 (0.66–1.61)	0.892
	Lorenzo-Betancor et al. [19]	Spain	226 (0.312)	1117 (0.277)	1.20 (0.88–1.63)	0.254
	Bourassa et al. [20]	France, Canada	259 (0.320)	479 (0.350)	0.87 (0.88–1.63)	0.408
	Radovica et al. [21]	Latvia	141 (0.298)	130 (0.304)	0.78 (0.47–1.30)	0.349
	Total group		2076 (0.371)	18,792 (0.344)	1.20 (1.05–1.36)	0.016
	Total group excluding Iceland discovery series		1624 (0.349)	4414 (0.318)	1.12 (0.99–1.27)	0.034