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LETTER TO THE EDITOR

Implication of the *LINGO2* gene in the predisposition to movement disorders

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ABSTRACT

Previous reports on the pathogenesis of age-related movement disorders, such as Parkinson's disease (PD) and essential tremor (ET), have demonstrated the potential implications of *LINGO1* (leucine-rich repeat and immunoglobulin domain-containing protein) gene. Although *LINGO2* has a high degree of homology with *LINGO1*, but it is less characterized and the role of *LINGO2* in the development of PD/ET remains unreported. Hence, this meta-analysis was conducted to evaluate the role of *LINGO2* in PD/ET pathogenesis. A total of 4 studies, which complied with the Hardy–Weinberg equilibrium, were included in the meta-analysis. Analysis of the pooled odds ratio and confidence interval of the studies were performed for five genetic models, namely: allelic, dominant, recessive, homozygous, and heterozygous. No significant association was observed between the *LINGO2* polymorphism and PD/ET, although subgroup analysis through conventional meta-analysis indicated that the recessive models of rs7033345 and rs10812774 are significantly associated with predisposition to ET in the Asian population. However, trial sequential analyses for both polymorphisms were unlikely to reveal any robust effect. Hence, studies with larger samples on this association are needed in the future to corroborate our results.

Dear editor,

Age-related movement disorders, such as Parkinson's disease (PD) and essential tremor (ET), affect 3%–6% and 1%–2% of the elder population, respectively [1]. Although the exact etiology remains elusive, however, several factors, including genetics and inflammation, have been reported to contribute toward the development of PD and ET [2]. The *LINGO* (Leucine-rich repeat and immunoglobulin domain-containing

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Abbreviations

ET	essential tremor	LRR	leucine-rich repeat
HWE	Hardy-Weinberg equillibirium	PD	Parkinson's disease
LINGO	leucine-rich repeat and immunoglobulin domain-containing protein		

protein) genes belong to a leucine-rich repeat (LRR) gene family which is composed of four members (*LINGO1–LINGO4*) [3]. Several of these genes have been implicated in the pathogenesis of PD and ET. A previous study [4] has observed a significantly higher LINGO1 protein expression in the cerebellum of patients with ET and PD relative to controls. Interestingly, although LINGO2 levels were also marginally higher in ET and PD cases, the difference was insignificant [4]. Results of the referred study are supported by a recently published article which emphasized that tremors induced by upregulated LINGO1 levels are modulated by the calcium-activated potassium (BK) channels [5]. This implies that a possible role for *LINGO1* in the pathogenesis of PD and ET. Furthermore, although several meta-analyses have demonstrated a lack of association between *LINGO1* gene polymorphisms and PD [6, 7], the latest analysis indicated a protective role of rs11856808 in PD [3].

In contrast to *LINGO1*, *LINGO2* is less characterized, despite its high degree of homology with *LINGO1* and its restricted expression in the neuronal tissue in comparison to *LINGO3/4* [1, 3]. Therefore, a meta-analysis of all eligible studies relating the *LINGO2* gene polymorphisms with a predisposition to PD/ET was conducted. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [8]. A literature search was conducted from PubMed, Scopus, and Web of Science, and was updated until 30 March, 2020. Keywords, such as "*LINGO2*", "PD", and "ET" were used in combination. The inclusion criteria of studies were as follows: (1) aims to evaluate the association between *LINGO2* gene polymorphisms and predisposition to PD/ET, and (2) conducted with a case-control design. Meta-analysis was performed for each gene polymorphism with two or more studies. Genotypic frequency of *LINGO2* gene polymorphism was tested for deviation from the Hardy–Weinberg equilibrium (HWE) in the control subjects.

The genetic association was assessed using five different genetic models, including allelic [mutant type (M) *vs.* wild type (W)], dominant (MM+WM *vs.* WW), recessive (MM *vs.* WM+WW), homozygous (MM *vs.* WW), and heterozygous (WM *vs.* WW) [2, 9]. The associations between *LINGO2* gene polymorphisms and predisposition to PD/ET were calculated based on pooled odds ratio (OR) and 95% confidence interval (CI). Z test was conducted to evaluate the significance of the pooled effect size. Heterogeneity among studies was evaluated using the Q test and I^2 statistic. A significant Q-statistic ($p < 0.10$) indicated heterogeneity across studies. The I^2 values indicated no (0–24.9%), low (25%–49.9%), moderate (50%–74.9%), or high (75%–100%) heterogeneity. The random-effects model was used if heterogeneity existed; otherwise, the fixed-effects model was used. Subgroup analysis was stratified by patient ethnicity. The p-value < 0.05 was indicative of the statistical significance. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of included studies, with good quality studies indicated by a cutoff score of ≥ 7 (see Supplementary Table 1). Trial sequential

Table 1 The characteristics of studies included on *LINGO2* gene polymorphism and Parkinson's disease (PD) or essential tremor (ET).

First Author, Year [Reference]	Disease	Country/ region	Ethnicity	Sample size (cases/controls)	Genotype (WW/WM/MM)		*p* value for HWE	NOS score
					Cases	Controls		
rs7033345	PD							
Chen et al, 2015 [3]		China	Asian	1055/810	349/507/199	263/415/132	0.137	8
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	615/624	332/240/43	347/227/50	0.966	8
Wu et al, 2011 # [11]		China	Asian	244/307	76/120/48	109/152/46	0.959	8
Wu et al, 2011 * [11]		Singapore	Asian	189/189	62/83/44	64/102/23	0.118	8
rs10812774	PD							
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	607/610	171/313/123	159/322/129	0.149	8
Wu et al, 2011 # [11]		China	Asian	244/307	64/127/53	88/158/61	0.513	8
Wu et al, 2011 * [11]		Singapore	Asian	188/190	61/92/35	61/100/29	0.250	8
rs13362909	PD							
Chen et al, 2015 [3]		China	Asian	1055/810	1024/31/0	778/31/0	0.578	8
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	612/625	547/59/6	564/59/2	0.730	8
rs10968280	PD							
Chen et al, 2015 [3]		China	Asian	1055/810	983/70/2	763/47/0	0.453	8
Su et al, 2012 [12]		Taiwan	Asian	457/378	425/32/0	342/35/1	0.916	8
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	633/642	506/103/7	482/136/6	0.287	8
rs7033345	ET							
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	1237/624	719/441/77	263/415/132	0.137	8
Wu et al, 2011 # [11]		China	Asian	129/307	42/62/25	109/152/46	0.554	8
Wu et al, 2011 * [11]		Singapore	Asian	198/189	64/97/37	64/102/23	0.204	8
rs10812774	ET							
Vilariño-Güell et al, 2010 [1]		USA	Caucasian	1193/610	324/641/228	159/322/129	0.149	8
Wu et al, 2011 # [11]		China	Asian	129/307	37/56/36	88/158/61	0.513	8
Wu et al, 2011 * [11]		Singapore	Asian	196/190	71/82/43	61/100/29	0.250	8

W, wild type; M, mutant type; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle–Ottawa scale. # indicates a subpopulation of Chinese subjectis, and * indicates a subpopulation of Singaporean subjects.

analysis (TSA) was performed for a significant result of conventional meta-analysis according to a previously published article [10]. We employed a significance of 5% for type I error, and a significance of 20% for type II error in order to calculate the required sample size, and build the TSA monitoring boundaries.

A total of four studies which investigated the association between *LINGO2* gene polymorphisms (rs7033345, rs10812774, rs13362909, and rs10968280) and PD/ET were retrieved from PubMed and Scopus databases [1, 3, 11, 12] and all of the single-nucleotide polymorphisms complied with the HWE ($p > 0.05$) (Table 1). Pooled results on the associations between *LINGO2* gene polymorphisms and predisposition to PD/ET are shown in Table 2. No significant association was observed between *LINGO2* gene polymorphisms and predisposition to PD/ET in all five inheritance models ($p > 0.05$, Table 2). Subgroup analysis based on ethnicity revealed that the recessive models, rs7033345 and rs10812774, are significantly

associated with predisposition to ET in the Asian population (Table 2). This is in line with a previous report from Wu et al. [11]. The result of TSA is shown in Fig. 1, with the required sample sizes being 1,651 and 1,403 samples for rs7033345 and rs10812774 under the recessive model, respectively (Fig. 1). The conventional meta-analysis for both polymorphisms has demonstrated statistical significance as the Z-curve lies outside the horizontal pink lines. However, TSA indicated that the cumulative Z-curve, for both polymorphisms, did not cross the trial

Table 2 Results of a meta-analysis of *LINGO2* gene polymorphism and Parkinson's disease (PD) or essential tremor (ET).

Groups	*N*	Allelic model		Dominant model		Recessive model		Homozygous model		Heterozygous model	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
PD											
rs7033345											
Pooled	4	0.96 (0.87–1.05)	0.434	0.93 (0.82–1.06)	0.330	0.85 (0.57–1.28)	0.460	0.86 (0.60–1.23)	0.415	0.93 (0.81–1.06)	0.312
Ethnicity											
Asian	3	0.90 (0.74–1.09)	0.308	0.93 (0.80–1.09)	0.431	0.76 (0.43–1.34)	0.347	0.76 (0.46–1.27)	0.307	0.94 (0.79–1.11)	0.516
rs10812774											
Pooled	3	0.99 (0.88–1.12)	0.979	0.96 (0.80–1.17)	0.741	1.03 (0.83–1.27)	0.746	1.00 (0.78–1.29)	0.947	0.95 (0.78–1.16)	0.640
Ethnicity											
Asian	2	1.07 (0.89–1.29)	0.416	1.06 (0.80–1.41)	0.666	1.17 (0.84–1.62)	0.341	1.19 (0.81–1.75)	0.349	1.02 (0.75–1.37)	0.893
rs13362909											
Pooled	2	1.01 (0.76–1.34)	0.932	0.96 (0.71–1.30)	0.824	–		–		0.92 (0.68–1.25)	0.609
rs10968280											
Pooled	3	0.93 (0.57–1.53)	0.795	0.91 (0.55–1.52)	0.740	1.19 (0.44–3.17)	0.727	1.13 (0.42–3.02)	0.805	0.90 (0.55–1.49)	0.707
Ethnicity											
Asian	2	1.03 (0.44–2.37)	0.941	1.03 (0.46–2.31)	0.939	1.21 (0.13–11.04)	0.860	1.21 (0.13–11.02)	0.861	1.03 (0.48– 2.18)	0.931
ET											
rs7033345											
Pooled	3	0.67 (0.19–2.34)	0.537	0.55 (0.11–2.61)	0.452	0.67 (0.11–4.06)	0.663	0.49 (0.03–6.02)	0.577	0.57 (0.16–1.97)	0.378
Ethnicity											
Asian	2	1.17 (0.95–1.43)	0.129	1.10 (0.81–1.49)	0.520	1.49 (1.01–2.20)	**0.042***	1.50 (0.97–2.31)	0.065	1.00 (0.72–1.37)	0.994
rs10812774											
Pooled	3	0.99 (0.88–1.11)	0.866	0.93 (0.77–1.11)	0.442	1.23 (0.79–1.90)	0.348	1.00 (0.79–1.26)	0.977	0.90 (0.74–1.09)	0.283
Ethnicity											
Asian	2	1.11 (0.90–1.36)	0.310	0.90 (0.66–1.23)	0.530	1.56 (1.09–2.21)	**0.012***	1.33 (0.89–2.00)	0.157	0.76 (0.54–1.06)	0.112

Bold values indicate statistically significant difference between cases and control; * indicates *p*-values previously reported by Wu et al. in 2011 [11]; *N* indicates the number of included studies.

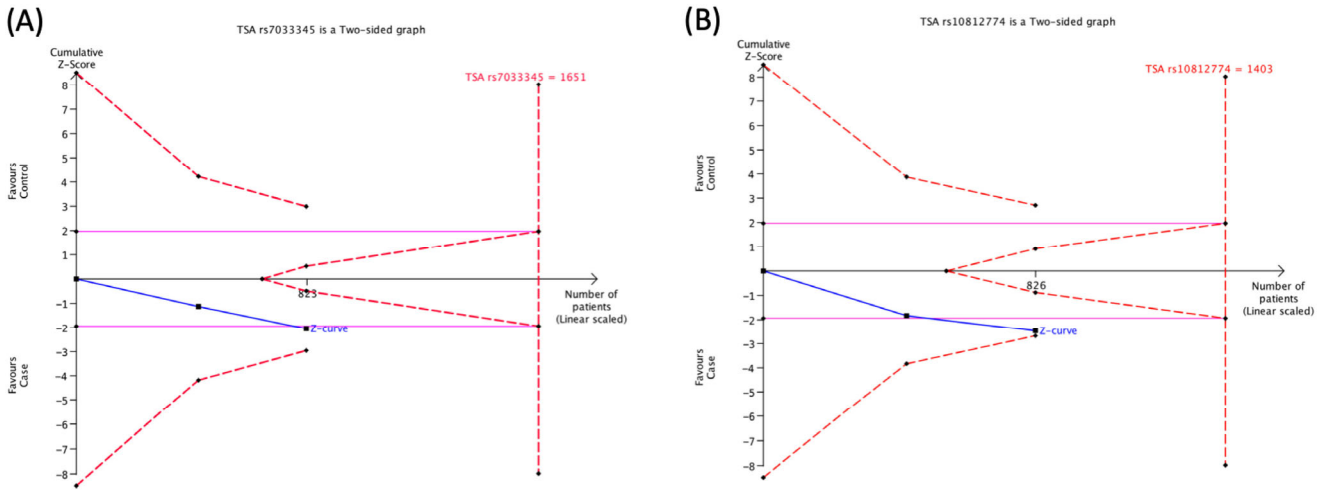

Fig. 1 Trial sequential analysis for *LINGO2* rs7033345 (A) and rs10812774 (B) polymorphism under the recessive model.

sequential monitoring boundary and did not reach the required sample size. Hence, both polymorphisms were unlikely to show a robust effect.

Therefore, our analysis indicated that rs7033345, rs10812774, rs13362909, and rs10968280 of *LINGO2* show no association with a predisposition to both PD and ET. However, the analysis did not exclude the possibility of an association between polymorphisms of rs7033345 and rs10812774 of *LINGO2* with the risk of ET in the Asian population. Therefore, there is a potential possibility that rs7033345 and rs10812774 may be useful as biomarkers for early ET detection in the Asian population. Future studies should assess haplotypes involving several mutations in the *LINGO2* gene of patients with either PD or ET. In addition, assessment should be carried out on other reported polymorphisms which could not be evaluated in the current analysis due to the limited number of studies. Furthermore, since our negative findings may be due to the limited sample size, cohort studies with larger sample sizes are warranted to validate our results.

Conflict of interests

The authors declare no conflict of interests.

Authors' contribution

ZSU, GVS, and CPG conceptualized the study; ZSU and GVS performed the review; ZSU, GVS, and CPG analyzed the data; ZSU and GVS wrote the first draft; all authors contributed to revising the manuscript.

References

[1] Vilariño-Güell C, Wider C, Ross OA, et al. LINGO1 and LINGO2 variants are associated with essential tremor and Parkinson disease. *Neurogenetics* 2010, **11**(4): 401–408.

[2] Ulhaq ZS, Garcia CP. Inflammation-related gene polymorphisms associated with Parkinson's disease: an updated meta-analysis. *Egypt J Med Hum Genet* 2020, **21**: 14.

[3] Chen Y, Cao B, Yang J, et al. Analysis and meta-analysis of five polymorphisms of the LINGO1 and LINGO2 genes in Parkinson's disease and multiple system atrophy in a Chinese population. *J Neurol* 2015, **262**(11): 2478–2483.

[4] Delay C, Tremblay C, Brochu E, et al. Increased LINGO1 in the cerebellum of essential tremor patients. *Mov Disord* 2014, **29**(13): 1637–1647.

[5] Dudem S, Large RJ, Kulkarni S, et al. LINGO1 is a regulatory subunit of large conductance, Ca^{2+} - activated potassium channels. *Proc Natl Acad Sci USA* 2020, **117**(4): 2194–2200.

[6] Agúndez JAG, Lorenzo-Betancor O, Pastor P, et al. LINGO1 rs9652490 and rs11856808 are not associated with the risk of Parkinson's disease: results of a meta-analysis. *Parkinsonism Relat Disord* 2012, **18**(5): 657–659.
[7] Wu YW, Wang XY, Xu W, et al. Genetic variation in LINGO-1 (rs9652490) and risk of Parkinson's disease: twelve studies and a meta-analysis. *Neurosci Lett* 2012, **522**(1): 67–72.
[8] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009, **6**(7): e1000097.
[9] Ulhaq ZS. Update on "Associations of estrogen receptor alpha gene polymorphisms with type 2 diabetes mellitus and metabolic syndrome: A systematic review and meta-analysis". *Horm Metab Res* 2020, **52**(1): 67–70.
[10] Meng JL, Wang S, Zhang M, et al. TP73 G4C14-A4T14 polymorphism and cancer susceptibility: evidence from 36 case–control studies. *Biosci Rep* 2018, **38**(6): BSR20181452.
[11] Wu YW, Prakash KM, Rong TY, et al. Lingo2 variants associated with essential tremor and Parkinson's disease. *Hum Genet* 2011, **129**(6): 611–615.
[12] Su FC, Chen CM, Chen YC, et al. LINGO-2 polymorphism and the risk of Parkinson's disease in Taiwan. *Parkinsonism Relat Disord* 2012, **18**(5): 609–611.

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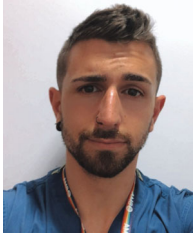

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