Serveur Académique Lausannois SERVAL serval.unil.ch

Author Manuscript
Faculty of Biology and Medicine Publication

This paper has been peer-reviewed but dos not include the final publisher proof-corrections or journal pagination.

Published in final edited form as:

serval
serveur académique lausannois

Unil
UNIL | Université de Lausanne
Faculté de biologie
et de médecine

LINGO1 and *LINGO2* variants are associated with essential tremor and Parkinson disease

Carles Vilariño-Güell,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Christian Wider,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA. Department of Neurology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Owen A. Ross,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Barbara Jasinska-Myga,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA. Department of Neurology, Medical University of Silesia, Katowice, Poland

Jennifer Kachergus,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Stephanie A. Cobb,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Alexandra I. Soto-Ortolaza,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Bahareh Behrouz,
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Michael G. Heckman,
Biostatistics Unit, Mayo Clinic, Jacksonville, FL, USA

Nancy N. Diehl,
Biostatistics Unit, Mayo Clinic, Jacksonville, FL, USA

Claudia M. Testa,
Emory Department of Neurology and Center for Neurodegenerative Diseases, Whitehead Biomedical Research Building, Atlanta, GA, USA

Zbigniew K. Wszolek,
Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

Ryan J. Uitti,
Department of Neurology, Mayo Clinic, Jacksonville, FL, USA

Joseph Jankovic,

Correspondence to: Matthew J. Farrer, Farrer.Matthew@mayo.edu.

Carles Vilariño-Güell and Christian Wider have contributed equally to this work.

Department of Neurology, Parkinson's Disease Center and Movement Disorders Clinic, Baylor College of Medicine, Houston, TX, USA

Elan D. Louis,
GH Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA. Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA. Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA. Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA

Lorraine N. Clark,
Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA

Alex Rajput, and
Division of Neurology, Royal University Hospital, University of Saskatchewan, Saskatoon, SK, Canada

Matthew J. Farrer
Department of Neuroscience, Mayo Clinic, 4500 San Pablo Road, Jacksonville, FL 32224, USA

Matthew J. Farrer: Farrer.Matthew@mayo.edu

Abstract

Genetic variation in the leucine-rich repeat and Ig domain containing 1 gene (*LINGO1*) was recently associated with an increased risk of developing essential tremor (ET) and Parkinson disease (PD). Herein, we performed a comprehensive study of *LINGO1* and its paralog *LINGO2* in ET and PD by sequencing both genes in patients (ET, *n*=95; PD, *n*=96) and by examining haplotype-tagging single-nucleotide polymorphisms (tSNPs) in a multicenter North American series of patients (ET, *n*=1,247; PD, *n*=633) and controls (*n*=642). The sequencing study identified six novel coding variants in *LINGO1* (p.S4C, p.V107M, p.A277T, p.R423R, p.G537A, p.D610D) and three in *LINGO2* (p.D135D, p.P217P, p.V565V), however segregation analysis did not support pathogenicity. The association study employed 16 tSNPs at the *LINGO1* locus and 21 at the *LINGO2* locus. One variant in *LINGO1* (rs9652490) displayed evidence of an association with ET (odds ratio (OR)=0.63; *P*=0.026) and PD (OR=0.54; *P*=0.016). Additionally, four other tSNPs in *LINGO1* and one in *LINGO2* were associated with ET and one tSNP in *LINGO2* associated with PD (*P*<0.05). Further analysis identified one tSNP in *LINGO1* and two in *LINGO2* which influenced age at onset of ET and two tSNPs in *LINGO1* which altered age at onset of PD (*P*<0.05). Our results support a role for *LINGO1* and *LINGO2* in determining risk for and perhaps age at onset of ET and PD. Further studies are warranted to confirm these findings and to determine the pathogenic mechanisms involved.

Keywords

Essential tremor; Parkinson disease; LINGO1; LINGO2; Genetic association

Introduction

Essential tremor (ET) and Parkinson disease (PD) are prevalent age-related movement disorders affecting about 3–6% (ET) and 1–2% of individuals over the age of 65 years (PD) [1–4]. While both ET and PD may cause significant motor impairment with tremor, they are regarded as distinct entities based on major differences at the clinical and pathological levels. ET patients display mostly symmetric action tremor which contrasts with asymmetric PD tremor that occurs at rest and is associated with bradykinesia, rigidity, and postural

instability. Pathologically, some ET cases have Purkinje cell loss and Purkinje cell axonal dilations (torpedoes) in the cerebellum [5]. Some cases have α-synuclein immunopositive Lewy bodies (LB) in the brainstem [5]. Conversely, in PD there is severe neuronal loss in brainstem nuclei with abundant LB pathology [5, 6]. Despite these differences, clinical evidence indicates an overlap exists between ET and PD with a fourfold increased risk of PD in patients with ET, increased prevalence of ET in relatives of patients with PD and the presence of action tremor often preceding the onset of PD symptoms [7]. Furthermore, imaging studies found signs of dopaminergic deficiency in some ET patients and brainstem LB have been reported in ET cases [8].

The leucine-rich repeat and Ig domain containing 1 gene (*LINGO1*) has recently been associated with an increased risk of developing ET and PD, providing the first evidence of a genetic link between the two diseases [9]. LINGO1 is a central nervous system-specific component of the Nogo-66 receptor (NgR1)/p75/LINGO1 signaling complex implicated in inhibition of oligodendrocyte differentiation, axonal myelination and regeneration, and neuronal survival [10–16]. Expression of *LINGO1* is increased after neuronal damage or cell death and its inhibition promotes functional recovery and axonal sprouting after spinal cord injury [10, 14, 17]. The expression of *LINGO1* is higher in the substantia nigra of patients with PD compared to age-matched controls and increases in ventral midbrain neurons in animal models of PD after neurotoxic lesions [10]. Furthermore, reduction of LINGO1 activity was shown to improve survival, growth, and function of dopaminergic neurons both in primary cell cultures and in vivo experimental models of parkinsonism in rodents [10, 18]. These data highlight the functional relevance of LINGO1 as a regulator of neuronal death, which is consistent with *LINGO1* variability altering the risk for ET and PD [9, 19, 20].

The leucine-rich repeat and Ig domain containing 2 gene (*LINGO2*) is a much less well characterized paralog of *LINGO1*. In contrast to the other *LINGO1* paralogs (*LINGO3* and *LINGO4*), *LINGO2* expression is detectable in the mouse adult brain and appears to be restricted to neuronal tissue [21, 22]. We recently performed a genome-wide association study in a PD patient-control series that identified single-nucleotide polymorphisms (SNPs) in *SNCA* and *LRRK2* associated with increased disease risk (unpublished findings). Although none of the SNPs in *LINGO2* were found to associate with PD after correction for multiple testing, nominal significant *P* values were observed. Given the high degree of homology between the LINGO1 and LINGO2 proteins (61%), and recently reported association studies, both *LINGO1* and its paralog *LINGO2* are reasonable candidate genes for ET and PD.

In the present study, we examine the role of *LINGO1* and *LINGO2* in ET and PD by sequencing both genes in a series of patients with ET (*n*=95) and PD (*n*=96), and by performing association studies in ET and PD patient-control series (combined *n*=2,522) using tagging SNPs (tSNPs) that capture >95% of the genetic variability of *LINGO1* and *LINGO2*. We identified ten rare coding variants (nine novel) in *LINGO1* and *LINGO2*; three of them did not segregate with disease within families. However, we found evidence suggesting *LINGO1* and *LINGO2* variation influences risk for and onset age of ET and PD, expanding the scope of genetic factors common to both diseases.

Methods

Study population

A total of 1,247 patients with ET, 633 patients with PD, and 642 control subjects of Caucasian origin from North America were included in this study (Mayo Clinic Jacksonville: 150 ET, 438 PD, and 423 controls; Emory University: 214 ET, 195 PD, and

219 controls; Columbia University: 449 ET; Baylor College of Medicine: 228 ET; and University of Saskatchewan: 206 ET). The control groups consisted of unrelated individuals and spouses free of known neurological disease. Demographics for each group are given in Table 1. All patients were examined by a movement disorders neurologist and diagnosed with PD according to published criteria [23] or satisfied clinical criteria for definite or probable ET [24]. All sites obtained local ethics committee approval prior to subject enrollment. Individuals were informed of all aspects pertaining to their participation in the study and gave either written or proxy consent.

DNA sequencing of LINGO1 and LINGO2

Genomic DNA was extracted from peripheral blood lymphocytes using standard protocols. Primer pairs for *LINGO1* and *LINGO2* (available on request) were used to sequence all coding exons and exon–intron boundaries by polymerase chain reaction (PCR) in 95 randomly selected ET and 96 PD probands from the Mayo Clinic Jacksonville. PCR products were purified from unincorporated nucleotides using Agencourt bead technology (Beverly, MA, USA) with Biomek FX automation (Beckman Coulter, Fullerton, CA, USA). Sequence analysis was performed as previously described [25]. All novel variants were examined for disease segregation when possible in affected and unaffected family members by additional sequencing.

Genetic association analysis

The population frequency of six known coding variants with minor allele frequency (MAF) <10% and six novel *LINGO1* and three *LINGO2* variants was assessed in the case-control series. Selection of additional tSNPs was based on HapMap Phase II data using Haploview software [26]. The regions containing *LINGO1* and *LINGO2* exons from any reported transcript (±2.5 kb surrounding noncoding exons or ±10 kb for coding exons) were used for the selection of tSNPs. In total 16 tSNPs across *LINGO1* and 21 across *LINGO2* loci were selected to capture >95% of the polymorphic variation in these regions (MAF>5% and r^2>0.8) in Caucasian population standards. Genotyping of tSNPs and of known and novel coding variants (MAF<10%), identified by sequencing, was performed on a Sequenom MassArray iPLEX platform (San Diego, CA, USA); all primer sequences are available on request. For each variant genotyping error was assessed by deviation from Hardy–Weinberg equilibrium expectation. All genotypes are given on the "+" strand.

Associations for PD and ET were evaluated using logistic regression models adjusted for age and gender; odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Single SNP associations with age at disease onset were examined using linear regression models adjusted for gender; regression coefficients and 95% CIs were estimated. Due to the alternate association findings in previous reports, both dominant (major allele homozygote vs minor allele homozygote and heterozygote) and recessive (minor allele homozygote vs major allele homozygote and heterozygote) models were considered in all regression analyses. *P* values<0.05 were considered significant, and no adjustment for multiple testing was performed in this exploratory study.

Results

Sequencing analysis in 95 ET and 96 PD patients identified six novel coding variants in *LINGO1* (Ser4Cys, Val107Met, Ala277Thr, Arg423Arg, Gly537Ala, and Asp610Asp) and three in *LINGO2* (Asp135Asp, Pro217Pro, and Val565Val; Fig. 1, Table 2). In addition five known polymorphisms were detected in *LINGO1* (rs2271398, rs2271397, rs2271396, rs3743481, and rs61737308), four of which with a MAF>10%. Three novel variants in *LINGO1* (Ser4Cys, Val107Met, and Gly537Ala) did not segregate with disease within

families (Fig. 2); two of these variants, Ser4Cys and Gly537Ala, as well as Ala277Thr, Arg423Arg, and Asp610Asp in *LINGO1* and Pro217Pro and Arg507His in *LINGO2* were observed exclusively in cases and not in controls (Table 2).

Results of single SNP associations with ET and PD are presented in Table 3. Whereas the original report and one replication study identified the minor allele of rs9652490 associated with an increased risk of ET [19, 20], we previously identified association with ET and PD for the major allele [9]. The association study of *LINGO1* tSNPs identified only the previously reported variant (rs9652490) being associated with both ET and PD under a recessive model (ET, OR=0.63, *P*=0.026; PD, OR=0.54, *P*=0.016). The risk allele found to be overrepresented in the disease groups was the major allele (T; genotype frequencies are provided in Supplemental Table 1). This association is consistent with our previous report [9] but in disagreement with other studies [19, 20]. The reasons for this alternate association are unclear, but several theoretical hypothesis have been proposed [27].

Additional associations with ET were identified for rs4886887, rs3144, rs8028808, and rs12905478 (Table 3), spanning the entire *LINGO1* gene (Fig. 1). Similarly to the previously described association with rs9652490, the major alleles of rs8028808 and rs12905478 were overrepresented in cases resulting in protective ORs for the minor alleles (OR=0.49 and 0.36, respectively). However, for rs4883887 and rs3144, the associations were driven by the minor alleles (OR=1.83 and 1.48, respectively). No additional tSNPs in *LINGO1* were found to be significantly associated with PD. The analysis of *LINGO2* tSNPs in ET resulted in only one variant (rs1412229) being associated with disease under a recessive model (OR=0.72, *P*=0.015). Similar results were obtained for rs10968280 and PD under a dominant model (OR=0.73, *P*=0.029; Table 3).

One variant in *LINGO1* (rs907396) was associated with a 5-year younger mean age at ET onset (*P*=0.019). Association with the age of PD onset identified two variants conferring a later age at onset by approximately 5 years when the minor allele was present in homozygote form (rs4886887, *P*=0.047; rs3144, *P*=0.024; Supplemental Table 2). An earlier age at onset for ET by 4 to 5 years was also observed for two variants in *LINGO2* (rs10812774 and rs7033345). In contrast, none of the variants in *LINGO2* were significantly associated with age at onset of PD, however a trend toward an association (0.05 *P* 0.07) was observed for four variants (rs9644872, rs11793421, rs4879257, and rs6476092; Supplemental Table 2).

Discussion

Progress in the field of neurodegenerative disorders has highlighted the interplay of combined genetic factors in determining risk for complex traits. While variability in several genes may influence the risk for developing one disease, single genes often affect the risk for more than one trait. This diversity is best exemplified by variability in the tau (*MAPT*) and α-synuclein (*SNCA*) genes which alters risk of PD (*MAPT* and *SNCA*), progressive supranuclear palsy and corticobasal degeneration (*MAPT*), and multiple system atrophy (*SNCA*) [28–31]. However, while a growing number of genes have been implicated in both sporadic and familial PD, genetic factors in ET have remained elusive [9, 32]. The *LINGO1* SNP rs9652490 was recently shown to associate with ET, a finding that was replicated independently and extended to PD [9, 19, 20]. Taken together with the established role of LINGO1 in neuronal survival and the preliminary evidence implicating *LINGO2* in PD, these data support *LINGO1* and *LINGO2* as candidate genes for ET and PD. In the present study, we examined this hypothesis by performing a comprehensive evaluation of both genes in a multicenter series of North American patients with ET and PD and in control subjects. The sequencing effort identified six novel coding mutations in *LINGO1* and three

in *LINGO2*. However, three of these variants did not display segregation with disease in three families including a multi-incident kindred with PD and ET. Identification of additional families will be required to examine segregation and assess pathogenicity of the other six novel variants. Although all nine novel variants were rare (MAF 0.16%), six of them were found only in patients and not in control subjects, indicating a possible role in pathogenesis that warrants further studies. Interestingly, three of the six variants found only in patients were identified in both ET and in PD, which supports the notion that genetic factors may influence both diseases simultaneously.

The association study using tSNPs identified one variant in *LINGO1* which alters the risk for both ET and PD (rs9652490), consistent with our previous report [9]. Interestingly, there is a discrepancy between the results of our two studies and those of others in which the association with disease was driven by the minor allele of rs9652490 [19, 20]. Possible explanations include population-specific differences, although the largest series used in the replication part of the initial report was ethnically similar to our patient-control series (US Caucasians) [19]. Four additional variants in *LINGO1* and one in *LINGO2* influenced the risk of ET, and one SNP in *LINGO2* altered the risk of PD. Furthermore, five variants in *LINGO1* and *LINGO2* had an effect on age at onset in ET (three variants) and PD (two variants). Despite the fact that these associations would not have withstood adjustment for the number of statistical tests performed and should therefore be considered exploratory, several lines of evidence are supportive including that: (1) *LINGO1* is biologically plausible as a candidate gene for neurodegenerative disease; (2) this is the fourth study by three independent groups in Caucasian and Asian populations that consistently nominate variants in *LINGO1* as a risk factor for developing ET; and (3) variants which display evidence of association with disease span the entire *LINGO1* gene. Factors contributing to our results not withstanding correction for multiple testing may include diagnostic inaccuracy (known to occur in both ET and PD), or the use of genetically heterogeneous, admixed North American populations. Power is unlikely to have played a major role as our combined ET series is the largest studied so far and our PD population is adequately powered to detect associations within the range of expected magnitude. Assuming a disease prevalence of 1%, an allele frequency of 0.25, and an OR of 2, we have >99% power to detect a dominant and 84% for a recessive association in our ET case-control study and a >99% dominant and 72% recessive association in PD.

A better molecular understanding of the pathogenesis for two prevalent movement disorders (ET and PD) will play a significant part in designing future therapeutic strategies aimed at prevention and cure. The results or our study support a role for *LINGO1* and *LINGO2* in determining risk for and onset age of ET and PD. Further replication studies on large and ethnically diverse populations are warranted to confirm these findings and to pave the way for the functional work that will unravel the pathogenic mechanisms involved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. de Rijk MC, Launer LJ, Berger K, Breteler MM, Dartigues JF, Baldereschi M, Fratiglioni L, Lobo A, Martinez-Lage J, Trenkwalder C, Hofman A. Prevalence of Parkinson's disease in Europe: a collaborative study of population-based cohorts. Neurologic diseases in the elderly research group. Neurology. 2000; 54:S21–S23. [PubMed: 10854357]

2. Louis ED, Thawani SP, Andrews HF. Prevalence of essential tremor in a multiethnic, community-based study in northern Manhattan, New York, NY. Neuroepidemiology. 2009; 32:208–214. [PubMed: 19169043]

3. Rajput AH, Birdi S. Epidemiology of Parkinson's disease. Parkinsonism Relat Disord. 1997; 3:175–186. [PubMed: 18591073]

4. Sur H, Ilhan S, Erdogan H, Ozturk E, Tasdemir M, Boru UT. Prevalence of essential tremor: a door-to-door survey in Sile, Istanbul, Turkey. Parkinsonism Relat Disord. 2009; 15:101–104. [PubMed: 18474448]

5. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, Pahwa R, Lyons KE, Ross GW, Borden S, Moskowitz CB, Lawton A, Hernandez N. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007; 130:3297–3307. [PubMed: 18025031]

6. Dickson DW. Alpha-synuclein and the Lewy body disorders. Curr Opin Neurol. 2001; 14:423–432. [PubMed: 11470957]

7. Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident Parkinson's disease and parkinsonism in essential tremor: a population based study. J Neurol Neurosurg Psychiatry. 2009; 80:423–425. [PubMed: 19289477]

8. Isaias IU, Canesi M, Benti R, Gerundini P, Cilia R, Pezzoli G, Antonini A. Striatal dopamine transporter abnormalities in patients with essential tremor. Nucl Med Commun. 2008; 29:349–353. [PubMed: 18317299]

9. Vilarino-Guell C, Ross OA, Wider C, Jasinska-Myga B, Cobb SA, Soto-Ortolaza AI, Kachergus JM, Keeling BH, Dachsel JC, Melrose HL, Behrouz B, Wszolek ZK, Uitti RJ, Aasly JO, Rajput A, Farrer MJ. LINGO1 rs9652490 is associated with essential tremor and Parkinson disease. Parkinsonism Relat Disord. 2009 Epub. 10.1016/j.parkreldis.2009.08.006

10. Inoue H, Lin L, Lee X, Shao Z, Mendes S, Snodgrass-Belt P, Sweigard H, Engber T, Pepinsky B, Yang L, Beal MF, Mi S, Isacson O. 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 USA. 2007; 104:14430–14435. [PubMed: 17726113]

11. Mi S, Lee X, Shao Z, Thill G, Ji B, Relton J, Levesque M, Allaire N, Perrin S, Sands B, Crowell T, Cate RL, McCoy JM, Pepinsky RB. LINGO-1 is a component of the Nogo-66 receptor/p75 signaling complex. Nat Neurosci. 2004; 7:221–228. [PubMed: 14966521]

12. Mi S, Miller RH, Lee X, Scott ML, Shulag-Morskaya S, Shao Z, Chang J, Thill G, Levesque M, Zhang M, Hession C, Sah D, Trapp B, He Z, Jung V, McCoy JM, Pepinsky RB. LINGO-1 negatively regulates myelination by oligodendrocytes. Nat Neurosci. 2005; 8:745–751. [PubMed: 15895088]

13. Li W, Walus L, Rabacchi SA, Jirik A, Chang E, Schauer J, Zheng BH, Benedetti NJ, Liu BP, Choi E, Worley D, Silvian L, Mo W, Mullen C, Yang W, Strittmatter SM, Sah DW, Pepinsky B, Lee DH. A neutralizing anti-Nogo66 receptor monoclonal antibody reverses inhibition of neurite outgrowth by central nervous system myelin. J Biol Chem. 2004; 279:43780–43788. [PubMed: 15297463]

14. Mi S, Hu B, Hahm K, Luo Y, Kam Hui ES, Yuan Q, Wong WM, Wang L, Su H, Chu TH, Guo J, Zhang W, So KF, Pepinsky B, Shao Z, Graff C, Garber E, Jung V, Wu EX, Wu W. LINGO-1 antagonist promotes spinal cord remyelination and axonal integrity in MOG-induced experimental autoimmune encephalomyelitis. Nat Med. 2007; 13:1228–1233. [PubMed: 17906634]

15. Shao Z, Browning JL, Lee X, Scott ML, Shulga-Morskaya S, Allaire N, Thill G, Levesque M, Sah D, McCoy JM, Murray B, Jung V, Pepinsky RB, Mi S. TAJ/TROY, an orphan TNF receptor family member, binds Nogo-66 receptor 1 and regulates axonal regeneration. Neuron. 2005; 45:353–359. [PubMed: 15694322]

16. 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; 18:3167–3182. [PubMed: 14686891]

17. Ji B, Li M, Wu WT, Yick LW, Lee X, Shao Z, Wang J, So KF, McCoy JM, Pepinsky RB, Mi S, Relton JK. LINGO-1 antagonist promotes functional recovery and axonal sprouting after spinal cord injury. Mol Cell Neurosci. 2006; 33:311–320. [PubMed: 17011208]

18. Mi S, Sandrock A, Miller RH. LINGO-1 and its role in CNS repair. Int J Biochem Cell Biol. 2008; 40:1971–1978. [PubMed: 18468478]

19. Stefansson H, Steinberg S, Petursson H, Gustafsson O, Gudjonsdottir IH, Jonsdottir GA, Palsson ST, Jonsson T, Saemundsdottir J, Bjornsdottir G, Bottcher Y, Thorlacius T, Haubenberger D, Zimprich A, Auff E, Hotzy C, Testa CM, Miyatake LA, Rosen AR, Kristleifsson K, Rye D, Asmus F, Schols L, Dichgans M, Jakobsson F, Benedikz J, Thorsteinsdottir U, Gulcher J, Kong A, Stefansson K. Variant in the sequence of the LINGO1 gene confers risk of essential tremor. Nat Genet. 2009; 41:277–279. [PubMed: 19182806]

20. Tan EK, Teo YY, Prakash KM, Li R, Lim HQ, Angeles D, Tan LC, Au WL, Yih Y, Zhao Y. LINGO1 variant increases risk of familial essential tremor. Neurology. 2009; 73:1161–1162. [PubMed: 19805735]

21. Haines BP, Rigby PW. Expression of the Lingo/LERN gene family during mouse embryogenesis. Gene Expr Patterns. 2008; 8:79–86. [PubMed: 18297755]

22. Homma S, Shimada T, Hikake T, Yaginuma H. Expression pattern of LRR and Ig domain-containing protein (LRRIG protein) in the early mouse embryo. Gene Expr Patterns. 2009; 9:1–26. [PubMed: 18848646]

23. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. Arch Neurol. 1999; 56:33–39. [PubMed: 9923759]

24. Louis ED, Ford B, Lee H, Andrews H, Cameron G. Diagnostic criteria for essential tremor: a population perspective. Arch Neurol. 1998; 55:823–828. [PubMed: 9626774]

25. Mata IF, Kachergus JM, Taylor JP, Lincoln S, Aasly J, Lynch T, Hulihan MM, Cobb SA, Wu RM, Lu CS, Lahoz C, Wszolek ZK, Farrer MJ. Lrrk2 pathogenic substitutions in Parkinson's disease. Neurogenetics. 2005; 6:171–177. [PubMed: 16172858]

26. Barrett JC, Fry B, Maller J, Daly MJ. Haploview: analysis and visualization of LD and haplotype maps. Bioinformatics. 2005; 21:263–265. [PubMed: 15297300]

27. Lin PI, Vance JM, Pericak-Vance MA, Martin ER. No gene is an island: the flip-flop phenomenon. Am J Hum Genet. 2007; 80:531–538. [PubMed: 17273975]

28. Goris A, Williams-Gray CH, Clark GR, Foltynie T, Lewis SJ, Brown J, Ban M, Spillantini MG, Compston A, Burn DJ, Chinnery PF, Barker RA, Sawcer SJ. Tau and alpha-synuclein in susceptibility to, and dementia in, Parkinson's disease. Ann Neurol. 2007; 62:145–153. [PubMed: 17683088]

29. Wider C, Vilarino-Guell C, Jasinska-Myga B, Heckman M, Soto-Ortolaza AI, Cobb SA, Aasly JO, Gibson JM, Lynch T, Uitti RJ, Wszolek ZK, Farrer MJ, Ross OA. Association of the MAPT locus with Parkinson's disease. Eur J Neurol. 2009 Epub. 10.1111/j.1468-1331.2009.02847.x

30. Peuralinna T, Oinas M, Polvikoski T, Paetau A, Sulkava R, Niinisto L, Kalimo H, Hernandez D, Hardy J, Singleton A, Tienari PJ, Myllykangas L. Neurofibrillary tau pathology modulated by genetic variation of alpha-synuclein. Ann Neurol. 2008; 64:348–352. [PubMed: 18661559]

31. Scholz SW, Houlden H, Schulte C, Sharma M, Li A, Berg D, Melchers A, Paudel R, Gibbs JR, Simon-Sanchez J, Paisan-Ruiz C, Bras J, Ding J, Chen H, Traynor BJ, Arepalli S, Zonozi RR, Revesz T, Holton J, Wood N, Lees A, Oertel W, Wullner U, Goldwurm S, Pellecchia MT, Illig T, Riess O, Fernandez HH, Rodriguez RL, Okun MS, Poewe W, Wenning GK, Hardy JA, Singleton AB, Gasser T. SNCA variants are associated with increased risk for multiple system atrophy. Ann Neurol. 2009; 65:610–614. [PubMed: 19475667]

32. Farrer MJ. Genetics of Parkinson disease: paradigm shifts and future prospects. Nat Rev Genet. 2006; 7:306–318. [PubMed: 16543934]

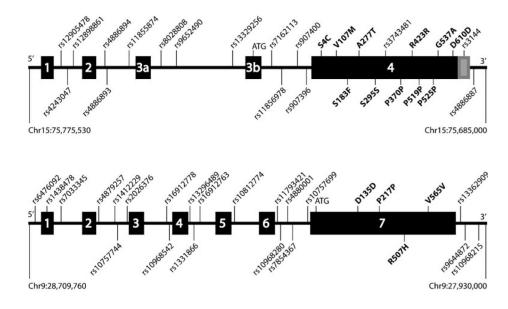**Fig. 1.**
Schematic representation of the *LINGO1* (*top*) and *LINGO2* (*bottom*) genes indicating the exons (*boxes*) and the variants studied. Novel (*above the genes*) and known (*below the genes*) coding variants are given in bold. For *LINGO1* exon arrangement was based on the two transcripts BC068558 and BC011057. The position of the start codon (*ATG*) was determined according to BC011057

Fig. 2.
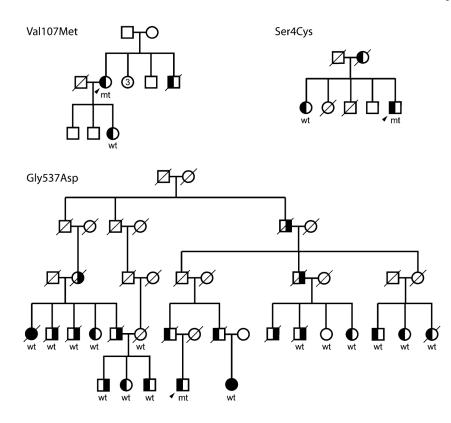Segregation analysis of three novel coding *LINGO1* variants in three pedigrees, representing males as *squares*, females as *circles*, whereas a *number inside a symbol* indicates the number of additional siblings. Patients with PD have *right-half-dark-filled symbols*, patients with ET have *left-half-dark-filled symbols*, deceased individuals are indicated with a *diagonal line*, and probands with an *arrow head*

Table 1

Demographic characteristics of patients and controls

	Controls	Essential tremor	Parkinson disease
No. of patients	642	1,247	633
Age	73±10 (33–101)	67±15 (9–97)	71±11 (30–92)
Male gender (*n*, %)	310 (48%)	530 (43%)	359 (57%)
Age at disease onset	N/A	50±20 (4–88)	62±12 (16–85)

The sample mean ± SD (range) is given for age and age at disease onset. Age at disease onset was only available in 396 ET and 423 PD cases

Table 2

Minor allelic counts and frequency for *LINGO1* and *LINGO2* coding variants

rs/ss number	Amino acid change	Controls	Essential tremor	Parkinson disease
LINGO1				
ss179321698	S4C	0	1 (0.04%)	1 (0.08%)
ss179321700	V107M	1 (0.08%)	1 (0.04%)	0
rs9855	S183F	0	0	0
ss179321701	A277T	0	2 (0.08%)	1 (0.08%)
rs34904447	S295S	0	0	0
rs61737308	P370P	18 (1.40%)	46 (1.84%)	21 (1.66%)
ss179321703	R423R	0	1 (0.04%)	0
rs61737307	P519P	0	0	0
rs11853548	P525P	0	0	0
ss179321704	G537A	0	3 (0.12%)	1 (0.08%)
ss179321705	D610D	0	2 (0.08%)	0
LINGO2				
ss179321693	D135D	3 (0.23%)	2 (0.08%)	2 (0.16%)
ss179321694	P217P	0	1 (0.04%)	0
rs17506843	R507H	0	2 (0.08%)	0
ss179321696	V565V	1 (0.08%)	1 (0.04%)	1 (0.08%)

Only those variants with a minor allele frequency over 10% were analyzed in this study

Table 3

Associations between tagging SNPs in *LINGO1* and *LINGO2* with ET and PD

| SNP (MA) | Essential tremor (n =1247) | | | | Parkinson disease (n=633) | | | |
| | Dominant | | Recessive | | Dominant | | Recessive | |
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
LINGO1								
rs4886887 (A)	0.91 (0.74, 1.13)	0.41	1.83 (1.11, 3.01)	0.018	0.95 (0.75, 1.21)	0.70	1.41 (0.80, 2.49)	0.23
rs3144 (G)	0.94 (0.77, 1.15)	0.52	1.48 (1.05, 2.08)	0.030	1.01 (0.80, 1.26)	0.96	1.25 (0.85, 1.85)	0.26
rs3743481 (T)	1.03 (0.84, 1.27)	0.78	1.08 (0.82, 1.42)	0.59	1.05 (0.83, 1.32)	0.70	1.06 (0.78, 1.44)	0.72
rs907396 (C)	1.03 (0.83, 1.27)	0.80	1.04 (0.78, 1.41)	0.78	1.00 (0.78, 1.27)	0.98	0.95 (0.67, 1.33)	0.74
rs907400 (G)	1.05 (0.84, 1.31)	0.70	1.29 (0.64, 2.58)	0.48	0.98 (0.76, 1.26)	0.85	0.72 (0.30, 1.70)	0.45
rs11856978 (C)	1.09 (0.85, 1.40)	0.51	1.45 (0.56, 3.77)	0.45	0.96 (0.72, 1.28)	0.77	1.50 (0.52, 4.28)	0.45
rs7162113 (T)	1.10 (0.90, 1.35)	0.37	1.24 (0.77, 1.99)	0.37	0.93 (0.74, 1.18)	0.56	0.89 (0.51, 1.54)	0.67
rs13329256 (T)	1.02 (0.76, 1.39)	0.88	2.73 (0.31, 24.12)	0.37	0.81 (0.57, 1.16)	0.25	4.74 (0.52, 42.95)	0.17
rs9652490[a] (C)	0.95 (0.77, 1.16)	0.61	0.63 (0.42, 0.95)	0.026	1.00 (0.79, 1.25)	0.98	0.54 (0.33, 0.89)	0.016
rs8028808 (T)	0.97 (0.78, 1.20)	0.76	0.49 (0.29, 0.83)	0.008	1.00 (0.78, 1.27)	0.97	0.59 (0.32, 1.08)	0.08
rs11855874 (C)	1.12 (0.89, 1.41)	0.33	1.03 (0.49, 2.15)	0.95	0.89 (0.68, 1.16)	0.37	1.14 (0.52, 2.50)	0.75
rs4886893 (A)	0.95 (0.78, 1.17)	0.66	1.10 (0.63, 1.93)	0.73	0.88 (0.70, 1.11)	0.29	1.19 (0.65, 2.19)	0.57
rs4886894 (C)	0.86 (0.70, 1.05)	0.14	1.00 (0.70, 1.41)	0.98	0.88 (0.70, 1.10)	0.27	1.08 (0.74, 1.59)	0.68
rs12898861(A)	1.15 (0.93, 1.43)	0.20	1.14 (0.88, 1.47)	0.32	1.01 (0.80, 1.29)	0.91	1.24 (0.94, 1.64)	0.13
rs4243047 (A)	0.95 (0.77, 1.16)	0.59	0.85 (0.64, 1.14)	0.27	0.90 (0.72, 1.13)	0.37	0.81 (0.58, 1.12)	0.20
rs12905478 (G)	0.88 (0.69, 1.13)	0.31	0.36 (0.16, 0.86)	0.021	1.00 (0.76, 1.31)	0.97	0.76 (0.33, 1.73)	0.51
LINGO2								
rs10968215 (A)	1.02 (0.83, 1.25)	0.87	1.14 (0.81, 1.61)	0.45	0.97 (0.77, 1.23)	0.81	0.88 (0.59, 1.32)	0.53
rs9644872 (C)	1.19 (0.96, 1.47)	0.12	1.02 (0.79, 1.32)	0.89	0.96 (0.76, 1.22)	0.75	0.91 (0.68, 1.21)	0.51
rs13362909 (A)	1.37 (0.99, 1.90)	0.06	1.84 (0.36, 9.25)	0.46	1.10 (0.76, 1.60)	0.62	2.76 (0.55, 14.01)	0.22
rs10757699 (C)	1.07 (0.87, 1.31)	0.55	0.97 (0.73, 1.28)	0.83	0.88 (0.70, 1.11)	0.30	0.81 (0.59, 1.12)	0.21
rs7854367 (A)	0.84 (0.66, 1.07)	0.15	1.27 (0.74, 2.20)	0.39	0.97 (0.74, 1.26)	0.79	1.57 (0.88, 2.80)	0.13
rs4880001 (G)	1.03 (0.83, 1.27)	0.79	1.12 (0.85, 1.47)	0.43	1.04 (0.82, 1.32)	0.76	0.91 (0.66, 1.25)	0.56
rs10968280 (T)	0.82 (0.64, 1.04)	0.11	1.85 (0.72, 4.73)	0.20	0.73 (0.55, 0.97)	0.029	1.28 (0.42, 3.87)	0.66
rs11793421 (G)	0.92 (0.72, 1.16)	0.47	0.94 (0.39, 2.29)	0.90	1.24 (0.96, 1.61)	0.10	1.97 (0.82, 4.70)	0.13
rs10812774 (A)	0.92 (0.73, 1.16)	0.46	0.90 (0.70, 1.16)	0.40	0.89 (0.69, 1.15)	0.37	0.95 (0.72, 1.26)	0.71

SNP (MA) *LINGO1*	Essential tremor (n =1247)				Parkinson disease (n=633)			
	Dominant		Recessive		Dominant		Recessive	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
rs16912763 (A)	0.82 (0.64, 1.06)	0.12	1.31 (0.50, 3.44)	0.59	1.06 (0.80, 1.40)	0.68	0.99 (0.31, 3.10)	0.98
rs1331866 (T)	1.08 (0.85, 1.36)	0.55	1.37 (0.59, 3.17)	0.46	0.83 (0.63, 1.09)	0.18	1.41 (0.56, 3.56)	0.47
rs13296489 (C)	1.03 (0.81, 1.30)	0.81	0.82 (0.64, 1.05)	0.12	0.95 (0.73, 1.23)	0.67	0.97 (0.74, 1.27)	0.81
rs10968542 (A)	1.00 (0.81, 1.24)	1.00	0.95 (0.73, 1.23)	0.70	0.99 (0.78, 1.26)	0.94	0.99 (0.74, 1.33)	0.95
rs16912778 (G)	1.22 (0.99, 1.51)	0.06	1.30 (0.99, 1.72)	0.06	0.96 (0.76, 1.22)	0.76	1.25 (0.92, 1.71)	0.15
rs2026376 (T)	1.12 (0.84, 1.51)	0.44	0.49 (0.17, 1.47)	0.21	1.03 (0.74, 1.44)	0.86	0.45 (0.12, 1.77)	0.25
rs10757744 (C)	1.05 (0.82, 1.33)	0.72	0.65 (0.32, 1.34)	0.24	0.99 (0.76, 1.30)	0.94	0.81 (0.37, 1.77)	0.59
rs1412229 (T)	1.08 (0.86, 1.35)	0.52	0.72 (0.55, 0.94)	0.015	0.81 (0.63, 1.03)	0.09	0.87 (0.65, 1.17)	0.35
rs4879257 (T)	0.90 (0.73, 1.10)	0.30	0.73 (0.48, 1.11)	0.14	1.09 (0.86, 1.38)	0.47	0.78 (0.48, 1.26)	0.30
rs7033345 (G)	0.85 (0.70, 1.04)	0.12	0.76 (0.52, 1.12)	0.17	1.06 (0.85, 1.33)	0.61	0.83 (0.54, 1.28)	0.39
rs1438478 (C)	0.81 (0.63, 1.04)	0.10	0.94 (0.44, 2.02)	0.87	0.99 (0.75, 1.30)	0.93	0.73 (0.29, 1.84)	0.50
rs6476092 (G)	0.91 (0.74, 1.12)	0.39	0.71 (0.45, 1.11)	0.13	1.09 (0.87, 1.38)	0.45	0.72 (0.43, 1.21)	0.21

Odd ratios (OR), 95% confident intervals (CI), and *P* values were obtained from logistic regression models adjusted for age and gender MA, minor allele

[a]Includes 428 control subjects, 353 ET, and 426 PD patients previously reported [9]