SUPPLEMENTARY MATERIAL FOR:

Variant in the sequence of the *LINGO1* gene confers risk of essential tremor

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This document includes Supplementary Methods, Supplementary Tables 1-4 and Supplementary Figures 1-3.

Supplementary Methods

Icelandic subjects.

In total, 487 familial and sporadic ET cases from Iceland were included in the study. Diagnosis was confirmed by history (patterned after Bain et al.[1]) and examination. Neurologists performed a physical examination on each patient with the aid of the TRIG criteria for definite tremor: bilateral postural tremor, with or without kinetic tremor, of hands or forearms, visible and persistent and lasting for at least five years. The exclusion criteria used were 1) the presence of other abnormal neurological signs, including dystonia and Parkinson's disease; 2) recent exposure to tremorogenic drugs or presence of drug or alcohol withdrawal; 3) neurological trauma within three months of the tremor; 4) clinical evidence for psychogenic origin of the tremor; 5) a history of dramatic onset of the tremor. Of the Icelandic cases, 338 had a relative with ET within three meiotic events. The remaining 149 cases were sporadic or missing ET diagnosis information for their relatives. The cases had a median age at onset of 20, a median age at study of 52, and 47% were male.

The 14,394 Icelandic controls included in the study were recruited as part of various genetic programs at deCODE and were not screened for ET. The controls came from genetic programs in the following diseases (approximate number of participants in brackets): addiction (1700), Alzheimer's disease (200), anxiety (500), asthma (700), attention deficit hyperactivity disorder (300), benign prostatic hyperplasia (300), breast cancer (600), chronic obstructive pulmonary disease (500), colorectal cancer (400), coronary artery disease (1400), dyslexia (400), endometriosis (100), enuresis (300), hypertension (900), infectious diseases (1300), longevity (400), lung cancer (100), melanoma (300), migraine (500), osteoporosis (1000), peripheral artery disease (500), polycystic ovary syndrome (300), pre-eclampsia (400), prostate cancer (500), psoriasis (300), restless legs syndrome (200), schizophrenia (300), sleep apnea (200), stroke (600), type II diabetes (500) and a set of population controls (300). Because some of the individuals used as controls were participants in more than one program, the numbers of participants in individual programs sum to more than 14,394. The controls had a median age at study of 55 and were 44% male. All work was approved by the relevant data protection and ethics committees in Iceland.

Austrian subjects.

The 77 Austrian ET patients were recruited through the movement disorders clinic at the Department of Neurology, Medical University of Vienna on a consecutive basis. The clinic of the department acts as a tertiary referral center with specialty clinics such as movement disorders, as well as a primary care facility for general neurology. All work was approved by the local ethics committee of the Medical University of Vienna and the Vienna General Hospital (AKH).

Diagnosis of ET was made based on established Movement Disorder Society (MDS) Consensus Criteria[2] (established to reduce diagnostic ambiguity) and all subjects were examined by a movement disorders neurologist. The diagnosis was made clinically; however, in cases of uncertainty, additional studies were performed to confirm the diagnosis (e.g. dopamine-transporter SPECT to rule out Parkinson's disease, electrophysiological testing including accelerometry and surface EMG to rule out enhanced physiological or psychogenic tremor). Patients included in the study were 18 years of age and older. Patients with the co-occurrence of

PD and ET were excluded, as were cases with a history of dystonia or any other secondary cause of tremor. The patients' median age at onset was 40, the median age at time of examination was 66.5, and 54% were male.

Control individuals (N = 342) were healthy blood donors from the same geographical region as the ET cases. They had a median age at study of 41 and 60% were male.

German subjects.

German ET patients (N = 69) were recruited from the movement disorder clinics at the Center of Neurology, University of Tuebingen, and at the Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-University. Patients were systematically examined and diagnosed by movement disorder specialists (F.A, M.D and L.S.). All patients were followed at least five years after the initial diagnosis. Patients who showed at referral or during follow-up clinical signs or imaging findings questioning the diagnosis of ET, such as progressive cerebellar dysfunction, parkinsonism, dystonia or MR abnormalities, were excluded. ET was therefore diagnosed according to established criteria. The German patients had a median age at onset of tremor of 50, a median age at study entry of 69 and were 45% male.

Controls were 176, all of European descent originating from the south of Germany. Neurological disorders were excluded by neurological examination at the time of blood sampling. The controls had a median age at study of 48 and were 48% male.

Informed consent of all participants was obtained and the genetic studies were approved by the local ethics committees.

American subjects.

All work was approved by the Emory Institutional Review Board (IRB). Informed consent was obtained from all subjects using IRB-approved consent forms and protocols. All enrollment work was done under the Clinical Research in Neurology (CRIN) protocol and consent. ET genotyping work was done under specific IRB protocols. Immediate and future research involving the use of DNA were specifically covered in the consent, as was contact for future research connected to the same study or different studies.

Case determination

Samples were drawn from either review of previously enrolled subjects in the CRIN database, or prospective enrollment of ET subjects into CRIN/ET observational and genetics work. CRIN provides an umbrella structure for subject enrollment in observational and genetic studies in Neurology, consent-approved data sharing across studies and disorders, and consistent sample processing. All subjects underwent a basic structured interview for demographics and family history. A Folstein Mini Mental Status Exam (MMSE)[3,4] was administered to all CRIN subjects by trained CRIN personnel supervised by a neuropsychologist per published guidelines.

All CRIN database subjects enrolled prior to January 2007 with a reported diagnosis of 333.1 (any tremor) were reviewed, as specifically approved in the consent. Detailed review was then done for all subjects consenting to future use of DNA samples. A research diagnosis was made by CMT using review of Emory movement disorders clinic visits, documented exams and medication responses, any outside medical records and the CRIN intake forms (providing a

handwriting sample as well as patient and family reporting of disease). ET subjects were then called in for full in-person assessments as below whenever possible.

ET subjects mid-2006 onward were recruited through IRB-approved ads in the Emory Movement Disorders and Neurosurgery deep brain stimulation group clinics, and ET community education events. ET subjects and family members were examined directly by at least one movement disorders specialist; two independent exams were obtained whenever possible. Exams included a tremor rating scale (TRS) derived from the Fahn-Tolosa-Marin scale and Tremor Research Group (TRG) scale items, the motor United Parkinson Disease Rating Scale (UPDRS), Tinetti gait and balance scales[5], tandem gait[6], and assessment for dystonia. Semi-structured interviews included ET specific questions derived from the Fahn-Tolosa-Marin scale and WHIGET studies[7].

CRIN review and new enrollment subjects were given a research diagnosis of ET using Movement Disorders Society (MDS) and TRG criteria[2,8,9]. ET cases were assigned possible, probable (80-99% certainty) or definite (>99% certainty) given the quality of data, disease duration, and tremor severity[2,10].

All individuals with definite or probable ET were included, both unrelated individuals and members from family groups, with specific pre-defined exceptions: we excluded cases carrying, in addition in ET diagnoses, either PD or dystonia diagnoses [2]. Subjects were excluded if an in-person exam and re-interview determined a different diagnosis, if movement disorders clinical notes listed an uncertain or different final diagnosis (i.e. medication induced tremor), or if there was a lack of sufficient exam, medication response, and other data to clearly establish an ET research diagnosis.

Finally, individuals who were estimated to have less than 90% European ancestry using the program STRUCTURE (see **Statistical Analysis** for additional information) were excluded. Altogether, 122 subjects were included. These patients had a median age at onset of 52, a median age at study of 70 and consisted of 43% males.

Included controls (N = 614) were also recruited at Emory University. They were self-reported European descent; in addition, individuals estimated to have less than 90% European ancestry (see **Statistical Analysis**) were excluded. The controls had a median age of 66 years and were 52% male.

Genotyping

Genome-wide arrays

The genome-wide study was carried out using the HumanHap300, HumanHap300-Duo and HumanCNV370-Duo BeadChips (Illumina). These three chips contained 314,125 SNPs in common. Prior to analysis, SNPs that were monomorphic, had yield less than 95% in either cases or controls, deviated from Hardy-Weinberg equilibrium or showed divergent allele frequencies between the chips were removed. This resulted in the exclusion of 8501 SNPs; thus, our final analysis was based on 305,624 SNPs. All samples included had a call-rate of greater than 98%.

Follow up SNP Genotyping – Iceland and Emory

Single SNP genotyping for the replication 798 samples from Emory as well as the 1,250 Icelandic samples used to type follow-up markers was carried out at deCODE genetics with the Centaurus (Nanogen, Bothell, WA, USA) platform. The quality of each Centaurus SNP assay was evaluated by genotyping each assay on the CEU samples and comparing the results with the

HapMap data. Assays with >1.5% mismatch rate were excluded and a linkage disequilibrium (LD) test was used for markers known to be in LD. Key markers from the genome-wide analysis were re-genotyped on more than 10% of samples and a mismatch was observed in less than 0.5% of samples.

Follow up SNP Genotyping Austria and Germany
Genotyping was performed in Austria using commercially available Taq Man-based allelic discrimination assays (Applied Biosystems) Standard procedures were used based on Applied Biosystems reagents and 20 ul reaction volumes. Allelic discrimination was assessed using an Applied Biosystems 7900 detection system.

Statistical Analysis.

Association analysis was carried out using a likelihood procedure described previously[11] ORs were calculated assuming a multiplicative model for risk. Association results from the various study groups were combined using the Mantel-Haenszel model. *P*-values were adjusted for relatedness and possible population stratification by dividing the chi-square statistics by an estimated inflation factor. In the case of the genome-wide typed samples, this inflation factor was estimated from the observed median chi-square statistic divided by 0.675[2]. For the Icelandic sample used for follow-up genotyping as well as the American sample from Emory, this factor was determined by a previously described simulation procedure[12].

For the American sample, we also used the program STRUCTURE[13] to estimate ancestry. Data from 30 microsatellite markers chosen for their informativeness of Caucasian, Asian and African ancestry were used and the program was run with the HapMap European (CEU), Asian (CHB+JPT) and African (YRI) individuals defined as training samples for three assumed populations.

Sequencing of *LINGO1* and *BC042092*.

All five exons of the *LINGO1* gene (OMIM: 609791, Ref Seq gene variants NM_032808.5 and *BC068558*, see exon structure in **Supplementary Figure 3**) and 3 exons from predicted gene *BC042092* (UCSC ID: uc002bcv.1) were sequenced in 93 Icelandic individuals. PCR amplifications and sequencing reactions were set up on SciClone ALH3000 robotic workstations (Caliper Life Sciences, Hopkinton, MA, USA) and amplified on MJR Tetrads (Bio-Rad Laboratories, Hercules, CA, USA).

Total reaction volume was 5 µL per well and contained 15 ng genomic DNA, 0.35 µM of each primer, 1 M Betaine (Sigma-Aldrich, St. Louis MO, USA), 2.5 mM MgCl2, 0.35 U of Taq DNA Polymerase and 0.5 µl of 10x buffer with $(NH_4)_2SO_4$ (Fermentas Inc, Ontario, Canada). PCR was performed under the following conditions: 94°C for 2 minute, followed by 40 cycles of 94°C for 30 seconds, 58°C for 30 seconds, 1 minute at 72°C and a final single step of 8 minutes at 72°C. PCR products were verified for correct length by agarose gel electrophoresis and purified with AMPure (Agencourt Bioscience, Beverly, MA, USA). Purified products were sequenced with an ABI PRISM Fluorescent Dye Terminator system (Applied Biosystems, Foster City, CA, USA) with a total reaction volume per well of 4 µL containing: 1 µL purified PCR product, 3 µL cycle sequencing mix containing 10X Buffer (800 mM TRIS-HCl pH: 9.0 and 20 mM MgCl2), either primer (0.35 µM) and BigDye version 3.0 at 1/32 strength. The cycle

sequencing reaction was run under the following conditions: 96°C for 1 minute, followed by 30 cycles of 96°C for 10 seconds, 50°C for 4 seconds and 60°C for 4 minutes. Dye terminator removal was set up on a SciClone ALH3000 liquid handling station on the entire cycle sequencing reaction volume, using 5 µL CleanSEQR (Agencourt), and resolved on Applied Biosystems 3730 capillary sequencers. SNP calling from primary sequence data was carried out with deCODE Genetics Sequence Miner software (deCODE Genetics, Reykjavik, Iceland). All variants identified by the automated systems were confirmed by manual inspection of primary signal traces. Primer sequences are listed in below.

Exon	Forward	Reverse
LINGO1.e1.a	AGCCTGGCTGGAGTGTCC	TGCCTGTGACCTTGACTGC
LINGO1.e1.b	CATCATTGCAGTCAAGGTCAC	GGAGGGAGTAAGAGGAGAGTCC
LINGO1.e1.c	GATCTGTCGGCTTCTATTAGGC	TGAGGATGAGGAGGATAGGG
LINGO1.e1.d	TAATAATACCCGCCCGAAGG	TGATGGTCCAGCTATTACCC
LINGO1.e1.e	CCCTCTTCATCTTCCCAACC	CCATCATCTGACACACGTACAG
LINGO1.e2	AAAGGGATCCTGACCGATAC	TTCCAGGGATCTTCCTTTGGTC
LINGO1.e3	GGGCTCATTCGCTAAACG	TGCTGGGAAGTGGGTAGG
LINGO1.e4	CGGAATTTGTTGGGGTTGG	GGCGGACAGACGGACAGC
LINGO1.e5.a	TCAGGATCCCCTTCAGGTCTA	GGACAGGTCTGCCGATGG
LINGO1.e5.b	CTCCAGCCCCTGGCTCTC	ACACGCGGCAGAGTCAAT
LINGO1.e5.c	GTGGGTGGGGCTGGAACC	CGCAAGTTCAACATGAAGATGATATG
LINGO1.e5.d	TGACTCTGCCGCGTGTCG	CAGCTACTCGCCCGACTG
LINGO1.e5.e	TGATGAGGGTCTTGATGTCG	AAGGACTTCCCTGATGTGCTAC
LINGO1.e5.f	TGAGACCAGGTGCTTTCG	TCTATCTCCGCTTCCTCAACC
LINGO1.e5.g	TTGCCAGAGACATTGAGCAC	GCGACAATGACCTCGTCTAC
LINGO1.e5.h	TTGAAGGAGTAGTCCCGGATG	AAGCGCTTTGTGGCAGTC
LINGO1.e5.i	GCTCACGATGTTCTCGTTG	AAGACTCCAGGCAGGGTAAG
BC042092.e1	AGGAGTGGGCGTGGTAGG	TAAACAGCCAGGCAGACG
BC042092.e2	CATTGTGACCTGTAAGGGACTC	GGGATGGAGATGAGCGAATA
BC042092.e3.a	ATGCCCTTCTTGTCCCTAAC	GGTGCTCCTTCAATGGTAAC
BC042092.e3.b	GGAAAGGAAAGGGCAGTC	CAGTCAACATGGGAGTAGAGC
BC042092.e3.c	GCAATGTCCACTCACACAACC	CCTTGGGAAATGGGTATGC
BC042092.e3.d	CCAAATGGGACAGAGATCC	GTCTGAAAGGCACTTCCCTATG
BC042092.e3.e	CCTGCTGCCCTGCTAAAC	AAACAGGCATTCCCACTGAC

Accession numbers and information on the SNPs identified through sequencing are provided in **Supplementary Table 3**.

Online databases:
Online Mendelian Inheritance in Man: LINGO1 (OMIM: 609791),
NCBI Reference Sequences (RefSeq): NM_032808.5
GenBank accession numbers: BC042092, BC068558
dbSNP accession numbers: ss105111441, ss105111440, rs10851895, ss105111439, ss105111442, rs11633842, ss105111438, ss105111437, ss105111436, ss105111443, ss105111435, ss105111434, rs2271398, rs2271397, rs2271396, rs3743481, rs11853396, rs3144, rs12438314, rs1058129.

Supplementary Table 1. Genome-wide association analysis for 452 ET cases and 14,394 controls. Two markers with *P*-values lower than 1×10^{-5} were tested for association in follow-up samples from Austria, Germany, the United States and Iceland. Allele T of marker rs11856808 was also associated with ET in the follow-up sample, although it was not significantly associated after adjusting for the effect of rs9652490 (**Supplementary Table 2**).

		Frequency			
Study Group [*N* cases/*N* controls]	**Marker[allele]**	**Cases**	**Controls**	**OR [95% CI]**	***P* value**
Discovery					
Iceland [452/14,378]	rs9652490[G]	0.329	0.230	1.63 [1.35,1.97]	3.0×10^{-7}
Iceland [451/14,385]	rs11856808[T]	0.451	0.352	1.51 [1.27,1.80]	3.0×10^{-6}
Follow-up					
Austria [77/342]	rs9652490[G]	0.292	0.193	1.73 [1.15,2.59]	0.0082
Austria [77/341]	rs11856808[T]	0.422	0.334	1.45 [1.01,2.08]	0.041
Germany [69/176]	rs9652490[G]	0.297	0.233	1.39 [0.89,2.17]	0.15
Germany [69/173]	rs11856808[T]	0.370	0.335	1.16 [0.77,1.76]	0.47
U.S. [119/611]	rs9652490[G]	0.273	0.222	1.32 [0.92,1.90]	0.14
U.S. [120/611]	rs11856808[T]	0.371	0.358	1.06 [0.76,1.46]	0.75
Iceland [35/290]	rs9652490[G]	0.271	0.224	1.29 [0.71,2.36]	0.41
Iceland [35/283]	rs11856808[T]	0.400	0.314	1.45 [0.84,2.51]	0.18
All follow-up [300/1,419]	rs9652490[G]	-	-	1.44 [1.16,1.78]	0.0010
All follow-up [301/1,408]	rs11856808[T]	-	-	1.23 [1.02,1.50]	0.035
Combined					
All combined [752/15,797]	rs9652490[G]	-	-	1.55 [1.35,1.79]	1.2×10^{-9}
All combined [752/15,793]	rs11856808[T]	-	-	1.39 [1.22,1.58]	7.7×10^{-7}

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Supplementary Table 2. Association results for marker rs9652490 and seven neighboring SNPs with $r^2 > 0.5$ with rs9652490 in the HapMap CEU. Results are shown for 487 ET cases and 649 controls from Iceland. *P*-values adjusted for the association of rs9652490 are given in the last column (*P*-adj). Four-hundred fifty two of the ET samples from the discovery sample are included in this Icelandic sample.

		Frequency				
Marker	**Allele**	**Cases**	**Controls**	**OR [95%CI]**	***P***	***P*-adj**
rs9652490	G	0.324	0.223	1.67 [1.34,2.09]	6.3×10^{-6}	1.0
rs13313467	A	0.324	0.228	1.63 [1.30,2.03]	1.8×10^{-5}	1.0
rs7177008	G	0.324	0.234	1.57 [1.26,1.96]	6.4×10^{-5}	1.0
rs11856808	T	0.447	0.350	1.50 [1.22,1.83]	0.00010	0.34
rs7176315	G	0.448	0.352	1.49 [1.22,1.83]	0.00011	0.38
rs11856876	C	0.447	0.355	1.47 [1.20,1.80]	0.00022	0.52
rs8028808	A	0.213	0.151	1.52 [1.17,1.98]	0.0018	0.49
rs11631120	G	0.218	0.166	1.40 [1.10,1.79]	0.0062	0.081

Supplementary Table 3. SNPs and in/dels identified through sequencing exons of the *LINGO1* gene. For highlighted SNPs with rs names, HapMap (CEU) minor allele frequency (MAF) is given. For the remaining markers, which include both new markers with ss names and rs SNPs without frequency in the HapMap CEU, MAF from 93 Icelandic tremor patients is given. Genomic position is taken from NCBI Build 36.

Marker	Variation	Minor allele	MAF	Genomic position	Location in gene	Change
ss105111441	G/A	A	0.01	75776529	5´untranslated	-
ss105111440	G/C	C	0.13	75776023	5´untranslated	-
rs10851895	C/G	G	0.35	75770175	5´untranslated	-
ss105111439	A/T	T	0.02	75770099	5´untranslated	-
ss105111442	-/C	C	0.08	75756682	5´untranslated	-
rs11633842	G/A	A	0.008	75728395	5´untranslated	-
ss105111438	T/C	C	0.01	75727810	5´untranslated	-
ss105111437	C/T	T	0.09	75727390	5´untranslated	-
ss105111436	G/A	A	0.04	75725908	5´untranslated	-
ss105111443	-/14bp ins	14bp ins	0.12	75725786	5´untranslated	-
ss105111435	T/C	C	0.01	75721442	5´untranslated	-
ss105111434	C/T	T	0.01	75721143	5´untranslated	-
rs2271398	G/A	G	0.33	75694839	exon	synonymous
rs2271397	T/C	T	0.429	75694830	exon	synonymous
rs2271396	C/G	C	0.442	75694590	exon	synonymous
rs3743481	G/A	A	0.328	75694200	exon	synonymous
rs11853396	C/G	G	0.22	75693286	3´untranslated	-
rs3144	T/C	C	0.292	75693259	3´untranslated	-
rs12438314	G/A	A	0.33	75692741	3´untranslated	-
rs1058129	A/G	A	0.33	75692716	3´untranslated	-

Supplementary Table 4. Linkage disequilibrium (LD) between rs9652490 and markers identified by sequencing exons of the *LINGO1* gene. For all markers, LD results from 93 Icelandic tremor patients are shown. Position is taken from NCBI Build 36.

Marker	**Position**	***D´***	r^2
ss105111441	75705293	1.00	0.003
ss105111440	75704787	0.82	0.184
rs10851895	75698939	0.37	0.137
ss105111439	75698863	0.42	0.002
ss105111442	75685446	1.00	0.164
rs11633842	75657159	1.00	0.072
ss105111438	75656574	1.00	0.010
ss105111437	75656154	0.46	0.011
ss105111436	75654672	1.00	0.017
ss105111443	75654551	0.91	0.216
ss105111435	75650206	1.00	0.007
ss105111434	75649907	1.00	0.003
rs2271398	75623603	0.20	0.010
rs2271397	75623594	0.20	0.010
rs2271396	75623354	0.15	0.006
rs3743481	75622964	0.06	0.003
rs11853396	75622050	0.84	0.110
rs3144	75622023	0.23	0.038
rs12438314	75621505	0.05	0.003
rs1058129	75621480	0.16	0.007

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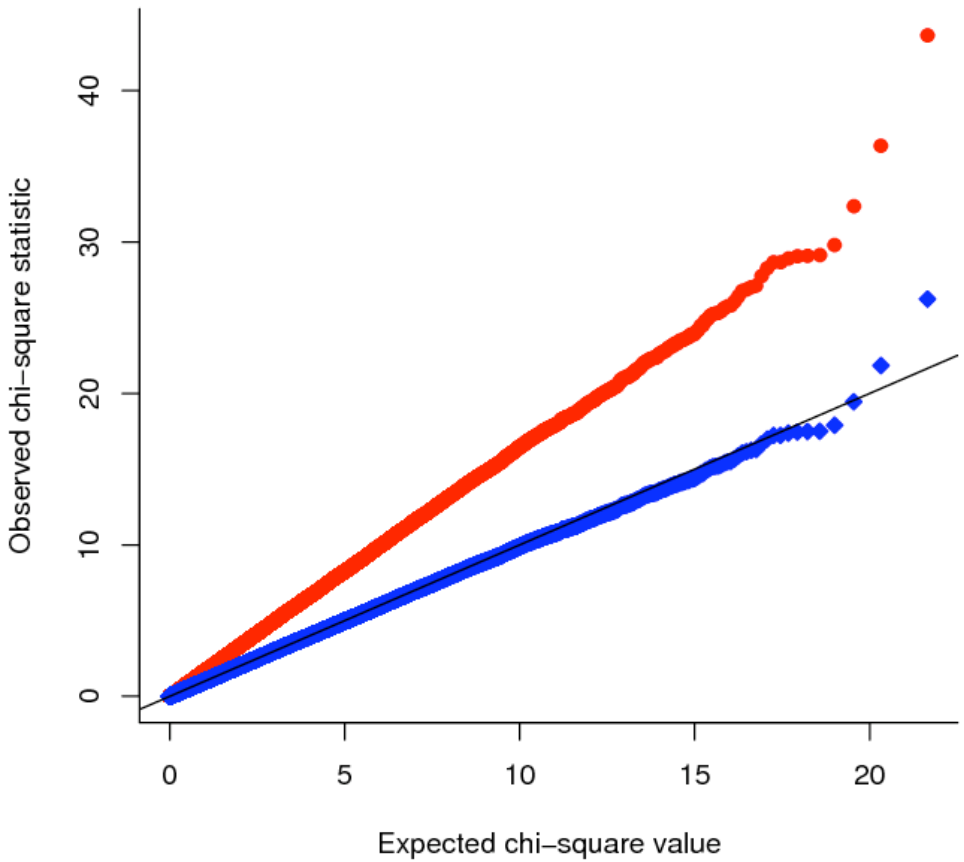

Supplementary Figure 1. Quantile-quantile plot of the 305,624 chi-square statistics from a genome-wide association analysis of 452 ET cases versus 14,394 controls. Both unadjusted chi-square statistics (red circles) and genomic-control adjusted chi-square statistics (blue squares) are shown.

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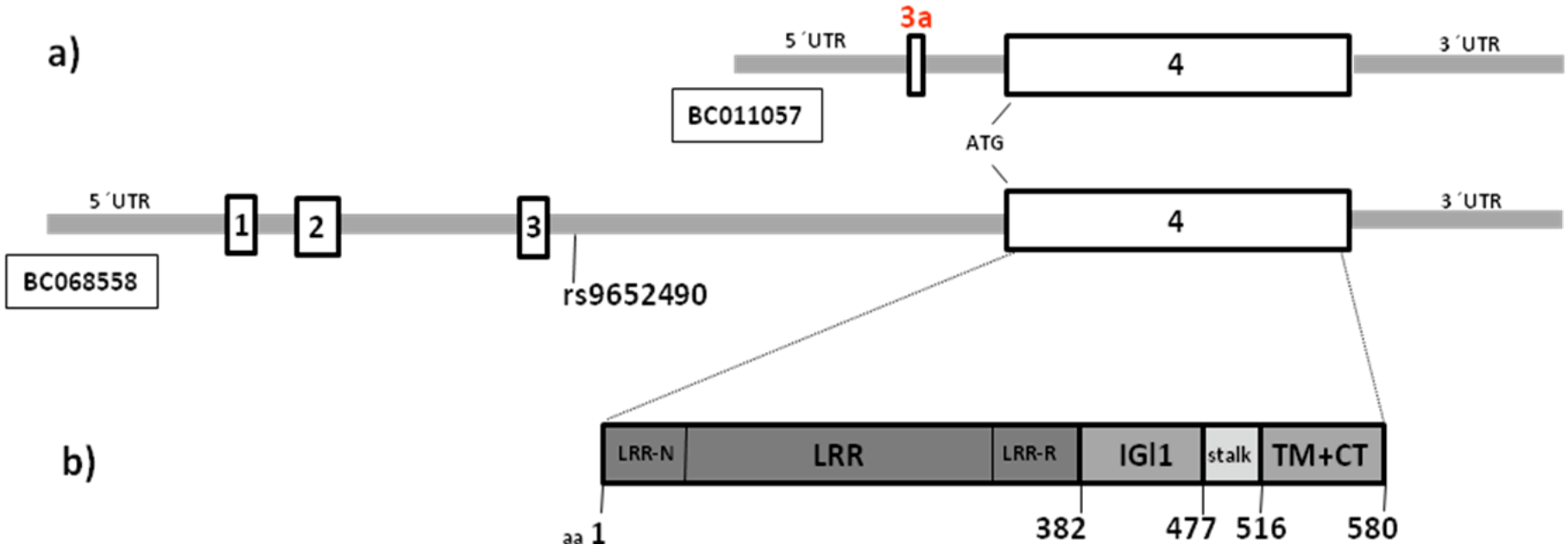

Supplementary Figure 2. Genetic structure **a)** and protein domains **b)** of the leucine-rich repeat neuronal 6A gene (*LINGO1*). Boxes represent exons. The single nucleotide polymorphism rs9652490, positioned in intron 3 is significantly associated with ET. This figure is not scaled. Domain organization of LINGO1 was re-drawn from Mosyak L et al.[14]: LRR (leucine-rich repeat); IGl1 (immuno-Globulin-like domain); stalk-region; TM (trans-membrane region); CT (cyto-plasmic tail).

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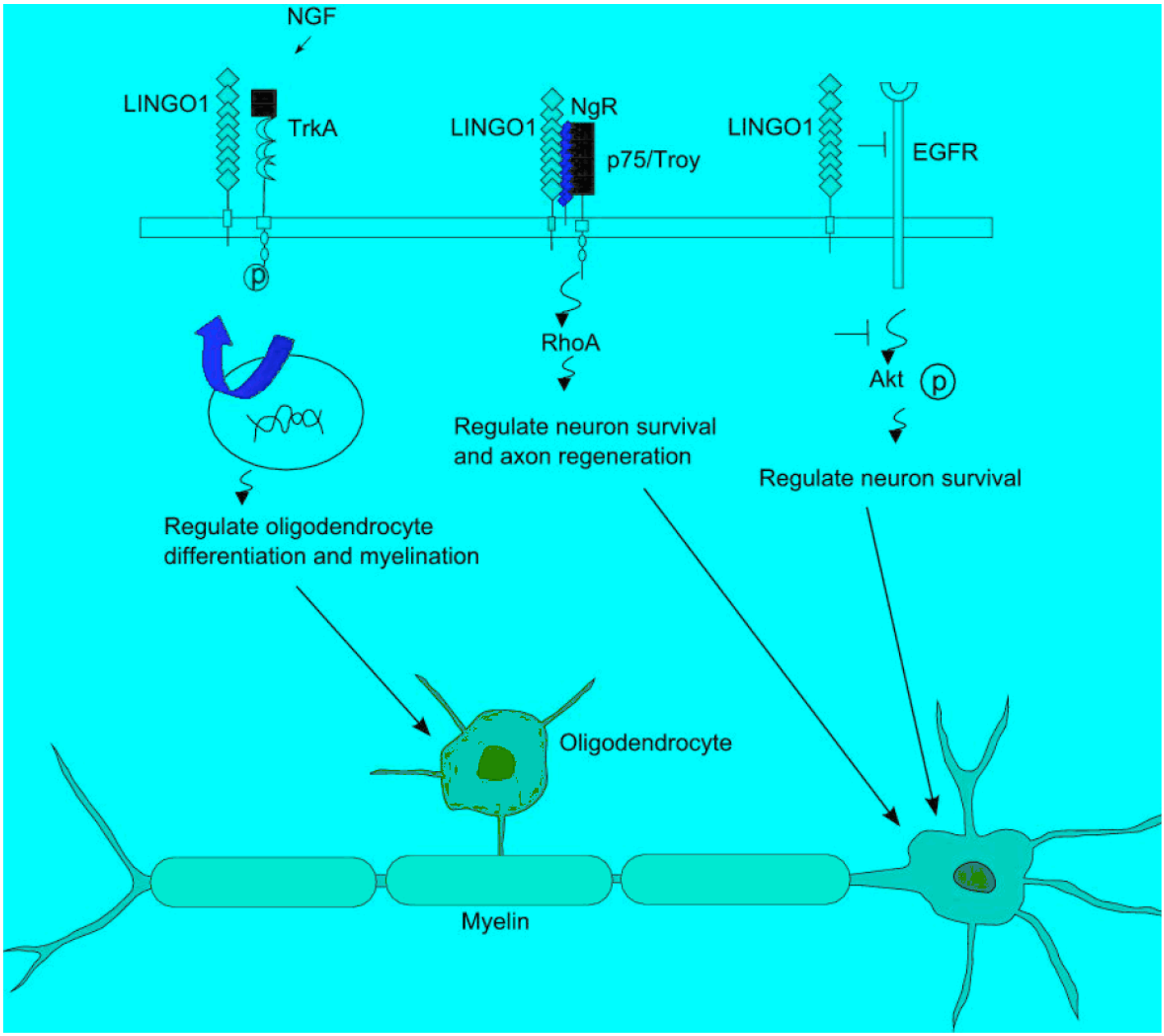

Supplementary Figure 3. Signaling pathways have been described for LINGO1**.** It has been shown that the gene is exclusively expressed in the central nervous system. It regulates axon generation, oligodendrocyte differentiation and myelination as well as neuron survival. Adapted and re-drawn from Mi S, et al.[15] with permission from the publisher.

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