REVIEW

# Genetic Risk Factors for Essential Tremor: A Review

Vasileios Siokas*, Athina-Maria Aloizou*, Zisis Tsouris*, Ioannis Liampas*, Paraskevi Aslanidou*, Metaxia Dastamani*, Alexandros G. Brotis†, Dimitrios P. Bogdanos‡, Georgios M. Hadjigeorgiou*,§ and Efthimios Dardiotis*

**Highlights**
In the current review, we thoroughly reviewed 74 identified articles regarding genes and genetic loci that confer susceptibility to ET. Over 50 genes/genetic loci have been examined for possible association with ET, but consistent results failed to be reported raising the need for collaborative multiethnic studies.

**Background:** Essential tremor (ET) is a common movement disorder, which is mainly characterized by bilateral tremor (postural and/or kinetic) in the upper limbs, with other parts of the body possibly involved. While the pathophysiology of ET is still unclear, there is accumulating evidence indicating that genetic variability may be heavily involved in ET pathogenesis. This review focuses on the role of genetic risk factors in ET susceptibility.

**Methods:** The PubMed database was searched for articles written in English, for studies with humans with ET, controls without ET, and genetic variants. The terms "essential tremor" and "polymorphism" (as free words) were used during search. We also performed meta-analyses for the most examined genetic variants.

**Results:** Seventy four articles concerning *LINGO1, LINGO2, LINGO4, SLC1A2, STK32B, PPARGC1A, CTNNA3, DRD3, ALAD, VDR, HMOX1, HMOX2, LRRK1,LRRK2, GBA, SNCA, MAPT, FUS, CYPsIL17A, IL1B, NOS1, ADH1B, TREM2, RIT2, HNMT, MTHFR, PPP2R2B, GSTP1, PON1, GABA receptors* and *GABA transporter, HS1BP3, ADH2, hSKCa3* and *CACNL1A4* genes, and ETM genetic loci were included in the current review. Results from meta-analyses revealed a marginal association for the STK32B rs10937625 and a marginal trend for association (in sensitivity analysis) for the LINGO1 rs9652490, with ET.

**Discussion:** Quite a few variants have been examined for their possible association with ET. LINGO1 rs9652490 and STK32B rs10937625 appear to influence, to some extent, ET susceptibility. However, the conflicting results and the lack of replication for many candidate genes raise the need for collaborative multiethnic studies.

**Keywords:** essential tremor; genetic polymorphism; single nucleotide polymorphism; variant; tremor; hyperkinetic movements; movement disorders

## Introduction

Essential tremor (ET) is a common movement disorder, which is mainly characterized by bilateral tremor (postural and/or kinetic) in the upper limbs, but can also spread to other parts of the body (e.g. jaw, head) [1, 2]. Phenotypically, ET is a tremor manifesting during voluntary movements, with a frequency of 4–12-Hz, and usually manifests as mildly asymmetric [3]. Alongside the motor manifestations, non-motor symptoms (e.g. REM-sleep behavior disorder, cognitive dysfunction, sensory abnormalities, dysautonomic symptoms, depression) may also be present [4–8].

ET compromises the commonest movement disorder of adulthood, while its onset may span from childhood to late ages [9]. Few environmental factors have been implicated as possible risk factors for ET [10–13]. Thus, the consumption of b-carboline alkaloid, caffeine and ethanol, harmane,

\* Department of Neurology, Laboratory of Neurogenetics, University Hospital of Larissa, Greece, Faculty of Medicine, School of Health Sciences, University of Thessaly, Larissa, GR

† Department of Neurosurgery, School of Medicine, University Hospital of Larissa, University of Thessaly, Larissa, GR

‡ Department of Rheumatology and Clinical Immunology, University General Hospital of Larissa, Faculty of Medicine, School of Health Sciences, University of Thessaly, Viopolis 40500, Larissa, GR

§ Department of Neurology, Medical School, University of Cyprus, Nicosia, CY

Corresponding author: Efthimios Dardiotis, M.D., PhD (edar@med.uth.gr)

exposure to pesticides, lead and other heavy metals, are all considered as potential risk factors for ET [10, 11, 13]. On the other hand, antioxidants and smoking may protect against ET [10, 11, 13]. However, the most widely established risk factors for ET are considered the family history of ET and aging [3, 12].

The exact pathophysiological processes that lead to ET are still poorly understood [14]. Despite the possible contribution of specific environmental factors in ET development, also genetic factors probably contribute to ET risk. The significance of genes to ET risk has been demonstrated via the identification of genetic variants from familial studies [15, 16], studies in twins [17], and the emerged variants derived from candidate gene association studies (CGASs) [18] and genome wide association studies (GWASs) [19–21].

In this review article we discuss the available scientific data regarding the role of genetics in ET, by giving emphasis to the results from CGASs. Moreover, we discuss the main findings from GWASs. We also performed meta-analyses for the most examined genetic variants. Our aim is to shed some light on which variants may predispose to ET.

## Methods –Study identification and selection
PubMed was searched for eligible studies written in English. We searched for articles from the inception of PubMed up to July 2019, for studies in humans, regarding ET and genetic variants. The terms used were "essential tremor" and "polymorphisms" as free words. The complete search algorithm can be accessed in the Supporting File 1. PubMed was searched for the last time on July 20th, 2019. Additionally, reference lists of retrieved articles were scanned for supplementary eligible articles. The flowchart with the selection process of the included studies is depicted in **Figure 1**. We included published articles between 1997 and 2019.

From each study, we extracted the following data when possible: 1) author, 2) year of publication, 3) ethnicity of the population, 4) numbers of cases and controls, 5) age at disease onset, 6) mean age of examination, 7) sex distribution, 8) genotyped variants, 9) family history of the participants, 10) diagnosis assessment, 11) correction for multiple comparisons, and 12) assessment of Hardy-Weinberg Equilibrium (HWE).
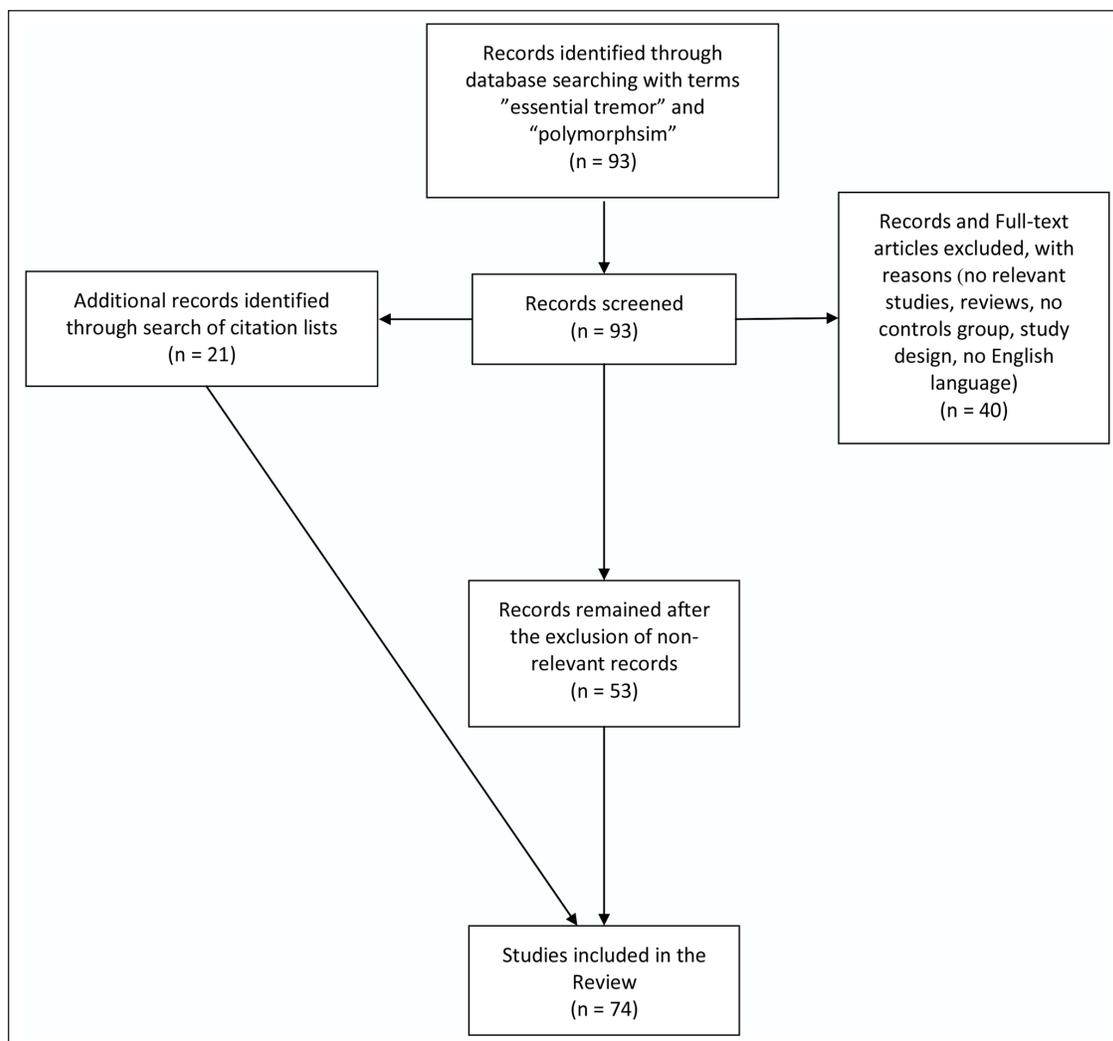


**Figure 1:** Flow chart presenting the selection of the studies included in the current review.

For the *LINGO1* rs9652490, *LINGO1* rs11856808, *SLC1A2* rs3794087, *STK32B* rs10937625 and *PPARGC1A* rs17590046 we performed meta-analyses. We included data from CGASs. Data from GWASs (neither from discovery nor from follow-up phases) were not included. The heterogeneity was calculated using the Cochran's Q and $I^2$ index. In case of high heterogeneity ($P_Q < 0.10$ and/or $I^2 > 75\%$), the random-effects model [22–24] was applied. Otherwise, the fixed-effects model [25] was used. Publication bias was estimated with Egger's test [26] when possible, with a p < 0.10 as suggestive of publication bias. The magnitude of association was calculated for the allelic model using the Review Manager (RevMan) Version 5.3 software (http://tech.cochrane.org/revman), with p < 0.05 as the statistically significant threshold. Allele counts were recalculated from data given as percentages, if necessary. For the analysis for LINGO1 rs9652490 and the studies of Vilarino-Guel et al. [27, 28], we included data only from the larger study [28], in order to avoid possible overlap. We also conducted a sensitivity analysis for LINGO1 rs9652490 by omitting one study at a time to examine the effect of each individual study.

## Results and Discussion
### *Literature Review*
Seventy four studies published between 1997 and 2019 were included in the current review. Baseline characteristics from the studies regarding *LINGO1*, *LINGO2*, *LINGO4*, *SLC1A2*, *STK32B*, *PPARGC1A*, *CTNNA3*, *DRD3*, *ALAD*, *VDR*, *HMOX1*, *HMOX2*, *LRRK1*, *LRRK2*, *GBA*, *SNCA*, *MAPT*, *FUS*, *CYPs*, *IL17A*, *IL1B*, *NOS1*, *ADH1B*, *TREM2*, *RIT2*, *HNMT*, *MTHFR*, *PPP2R2B*, *GSTP1*, *PON1*, *GABA receptors* and *GABA transporter*, *HS1BP3*, *ADH2*, *hSKCa3* and *CACNL1A4* genes, and ETM genetic loci, are accessible in Supporting File 2. Gene, chromosome position, possible mechanism of function, total number of studies (with comparison between ET cases and Controls), number of studies with association, number of studies without association and sample characteristics for the most examined genes (*LINGO1*, *DRD3*, *SLC1A2*, *LRRK2*, *FUS/TLS*, *SNCA*, *MAPT*, *HMOX1*, *HMOX2*) for association with ET, are presented at **Table 1**.

### 1. LINGO (LINGO 1, LINGO 2 and LINGO 4) genes
#### 1.1. LINGO 1 (Leucine rich repeat and Immunoglobulin-like domain-containing protein 1)
LINGO1 is thought to be implicated in neurite outgrowth, axonal regeneration, regulation of the myelination and neuronal survival [19], while its inactivation seems to protect from degeneration and enhance the survival of the neurons [3, 29, 30]. Published data indicate that defective function of LINGO1 may lead to Purkinje cell loss and axonal dysfunction, and therefore, possibly to ET [19, 31, 32].

The rs9652490 and the rs11856808, located in intron 3 across the *LINGO1* gene, were the two first variants that emerged as potential risk factors for ET through the first GWAS conducted in patients with ET [19]. In greater detail, the G allele of the rs9652490 was associated with ET in the initial discovery analysis of an Icelandic population [Odds

Ratio (OR) = 1.63, p = $3 \times 10^{-7}$], and in the combined sample of follow-up, which consisted of Austrian, German, American and Icelandic datasets. Most importantly, it reached the genome-wide significant association threshold in both of the analyses, in the discovery and the follow-up data-sets. The association of the rs9652490 and ET was further replicated in a few CGASs, in North American Caucasians [27, 28] [for the major allele (p = 0.014, OR = 2.2) [27] and (p = 0.026, OR = 0.63 for recessive model) [28]], North Americans (Non-Hispanic whites) (in patients with 'definite' or 'probable' ET (p = 0.03, OR = 1.41) [31], Asian (p = 0.00036, OR = 2.59) [33], German (p = 0.009, OR = 1.61) [20] and French (p = 0.046, OR = 1.70) [20] samples. However, the positive results were not reproduced in Spanish [34], Chinese [35, 36], Asian [37], Latvian [38] and French-Canadian [39] populations.

The other variant that emerged as a possible risk factor for ET through the GWAS from Stefansson et al., was the T allele of the rs11856808. It was associated with ET in the initial discovery analysis of the Icelandic population (OR = 1.51, p = $3 \times 10^{-6}$), but in the follow-up sample this association with ET was not revealed after adjustment for the rs965249 [19]. Overall, the results from the CGASs, following this GWAS, failed to replicate these results suggesting that rs11856808 is not a major genetic risk factor for ET [31, 34, 35, 38, 39], as it was found to confer susceptibility to ET only in German and French populations [20].

Apart from rs9652490 and rs11856808, some other *LINGO1* variants have also been associated with ET. Rs2271397 (p = 0.017, OR = 2.139), ss491228439 (p = 0.038, OR = 1.812) and the A465-C474-C714 haplotype (p = 0.041, OR = 1.8) were associated with increased ET risk in females of a Chinese Han population [36]. Rs7177008, rs13313467 and rs8028808, were associated with early-onset ET (p = 0.028, OR = 1.52; p = 0.0238, OR = 1.54; and p = 0.0391, OR = 1.55, respectively) in North Americans (Non-Hispanic whites) [31], while rs4886887 (OR = 1.83, p = 0.018 for recessive model), rs3144 (OR = 1.48, p = 0.03 for recessive model), rs8028808 (OR = 0.49, p = 0.008 for recessive model), and rs12905478 (OR = 0.36 p = 0.02) were associated with ET, with rs907396 influencing age at onset of ET (p = 0.019), in North America Caucasians [28]. Finally, rs8030859 was associated with ET in Germans (OR = 1.72, p = 0.00105) [40].

#### 1.2. LINGO 2 (Leucine rich repeat and Immunoglobulin-like domain-containing protein 2)
The LINGO2 protein presents high homology (over 50%) to LINGO1, but constitutes a much less characterized paralog [28, 41]. Despite the unknown function of LINGO2, it is considered to share some functions with LINGO1 and was therefore a target in ET CGASs. However, based on studies in mice, LINGO2 appears to be restricted to neuronal tissue [42], a feature that may differentiate it from the LINGO3 and the LINGO4 paralogs [28].

Two studies so far have examined the effect of *LINGO2* in ET, concerning a few variants [28, 41]. Of these, rs10812774 and rs7033345 have been shown to influence the age at onset of ET, as carriers of these variants appear to have an

**Table 1:** Gene, chromosome position, possible mechanisms of function, total number of studies (with comparison between ET cases and Controls), number of studies with association, number of studies without association and sample characteristics for the most examined genes for association with ET (Data from GWASs not included).

| Gene | Chromosome position*1 | Possible Mechanisms | Number of studies | | | Studies with association | | | | Studies without association | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Total | With association | Without association | In Caucasians/North Americans | In Asians | Total Cases | Total Controls | In Caucasians/North Americans | In Asians | Total Cases | Total Controls |
| LINGO1 | Chromosome 15: 77,613,027–77,820,900 | neurite outgrowth, axonal regeneration, regulation of the myelination and neuronal survival | 11 | 7 | 4 | 5 | 2 | 2,751 | 3,073 | 2 | 2 | 711 | 2,186 |
| DRD3 | Chromosome 3: 114,128,652–114,199,407 | dopamine receptor | 8 | 3 | 5 | 3 | 0 | 507 | 516 | 4 | 1 | 919 | 1,266 |
| SLC1A2 | Chromosome 11: 35,251,205–35,420,063 | regulates glutamate at synaptic cleft and extracellularly | 5 | 2 | 3 | 0 | 2 | 630 | 2,204 | 2 | 1 | 749 | 1,657 |
| LRRK2 | Chromosome 12: 40,196,744–40,369,285 | elevated LRRK2 kinase activity leads to neuronal toxicity | 5 | 1 | 4 | 0 | 1*2 | 450 | 827 | 1 | 3 | 1,165 | 3,650 |
| FUS/TLS | Chromosome 16: 31,180,110–31,194,871 | ALS and FTD pathways | 5*3 | 1 | 4 | 0 | 1 | 513 | 6,169 | 3 | 1 | 729 | 1,251 |
| SNCA | Chromosome 4: 89,724,099–89,838,315 | PD pathways | 3 | 1 | 2 | 1 | 0 | 46 | 100 | 2 | 0 | 767 | 1,406 |
| MAPT | Chromosome 17: 45,894,382–46,028,334 | PD pathways | 3 | 1 | 2 | 1 | 0 | 356 | 409 | 2 | 0 | 449 | 528 |
| HMOX1 | Chromosome 22: 35,380,361–35,394,207 | heme catabolism, lead toxicity | 3 | 1 | 2 | 1 | 0 | 202 | 747 | 1 | 1 | 427 | 447 |
| HMOX2 | Chromosome 16: 4,474,690–4,510,347 | heme catabolism, lead toxicity | 3 | 2 | 1*4 | 2 | 0 | 404 | 965 | 0 | 1 | 225 | 229 |

ET, essential tremor; LINGO1, leucine-rich repeat and Ig domain containing nogo receptor-interacting protein 1; SLC1A2, solute carrier family 1 member 2; LRRK2, leucine-rich repeat kinase-2; FUS/TLS, Fused in Sarcoma/Translocated in Liposarcoma; DRD3, dopamine D3 receptor; SNCA, a-synuclein; MAPT, microtubule associated protein tau; HMOX1, Heme Oxygenase 1; HMOX2, Heme Oxygenase 2; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; PD, Parkinson's disease; GWASs, genome-wide association studies.

* Based on https://www.ensembl.org/index.html.

*2 90% Asians.

*3 Rajput et al. (2014) and Merner et al. (2012) are not included.

*4 The interaction of ALAD rs1800435 with the HMOX2 rs1051308 could be weakly associated with the familial ET.

earlier age at onset by 4 to 5 years in a study on Caucasians from North America [28], while they were also associated with ET (OR = 1.50, p = 0.04 for rs7033345 and OR = 1.56, p = 0.01 for rs10812774 in recessive model) in Asians from Singapore [41]. Moreover, the rs1412229 has been associated with ET (OR = 0.72, p = 0.015 in recessive model) [28].

### 1.3. LINGO 4 (Leucine rich repeat and Immunoglobulin-like domain-containing protein 4)

The LINGO4 protein is another paralog of the LINGO1 protein, with an amino acid resemblance to LINGO of almost 50% [43]. One study has so far examined the role of two variants [the T>A transition (rs61746299), driving the amino acid change Thr444Ser, and the C>T transition (rs1521179), located 12 bp downstream to the end of coding region) across *LINGO4* gene variants in Chinese Han patients from Mainland China, failing to reach statistical significance, though [44].

### 2. SLC1A2 (Solute carrier family 1 – glial affinity glutamate transporter-member 2)

The solute carrier family 1 – glial affinity glutamate transporter-member 2 (SLC1A2) gene, [also known as Excitatory amino acid transporter 2 (EATT2) or glutamate transporter 1 (GLT-1)], encodes SLC1A2, a member of the group of solute transporter proteins [45]. Elevated levels of glutamate in the synaptic cleft and extracellularly are neurotoxic and have been associated with neurodegeneration. Defective function of SLC1A2 can lead to increased glutamate levels, and consequently to neurotoxicity [46]. A relation between SLC1A2 and ET can be found when one examines the pathophysiology of other factors in ET; the fact that ethanol relieves ET, while it increases the SLC1A2 expression, highlights the protein's importance, as well the elevated expression of SLC1A2 in the inferior olive where are produced the oscillations responsible for the tremor [6, 20, 47–49].

The second GWAS exploring the genetics of ET in participants from Germany, Austria, and Denmark, reported that the rs3794087 across the *SLC1A2* was associated with ET (OR = 1.46, p = $6.95 \times 10^{-5}$) [20]. The statistical significance was evident in both stages of the GWAS, as well in the subgroup analysis in ET patients with a 'definite' diagnosis [20], revealing the robustness of the results.

Since then, 5 further GCASs attempted to replicate the finding of this GWAS, in China, North America, Taiwan and Spain [50–54]. Based on these results, the *SLC1A2* rs3794087 A allele was more frequent in ET patients compared to controls in Taiwanese [53] and Chinese groups [51]. Based on the previous reports, it is however rather unlikely that the *SLC1A2* rs3794087 consists a major risk factor for ET.

### 3. STK32B (serine/threonine kinase 32B), PPARGC1A (PPARG Coactivator 1 Alpha), CTNNA3 (Catenin Alpha 3)

The third GWAS (two-stage) conducted so far, exploring the genetic susceptibility of ET included 2807 patients with ET and 6441 controls of European ancestry. Two markers, rs10937625 (OR = 0.77, p = $7.36 \times 10^{-4}$), located in the serine/threonine kinase *STK32B* gene, and rs17590046 (OR = 0.75, p = $6.81 \times 10^{-4}$) in the transcriptional coactivator *PPARGC1A* gene, were associated with ET [21]. Moreover, three markers, namely rs12764057 (OR = 1.17, p = $1.19 \times 10^{-8}$), rs10822974 (OR = 1.16, p = $1.65 \times 10^{-7}$) and rs7903491 (OR = 1.10, p = $2.49 \times 10^{-7}$), in the cell-adhesion molecule *CTNNA3* gene were found to be statistically significant in the combined analysis of both stages [21]. The C allele of rs10937625 of the *STK32B* gene was named a protective factor and the G allele of rs7903491 of the *CTNNA3* gene a risk factor for ET in Chinese [55], while the *PPARGC1A* gene was also associated with ET in Asians [56]. However, other studies failed to replicate the results for *STK32B* (rs10937625), *PPARGC1A* (rs17590046) and *CTNNA3* (rs12764057 and rs10822974) [55, 56].

### 4. DRD3 (Dopamine D3 receptor), ETM1, ETM2 and ETM3 loci

The rs6280, (also known as 312G>A and Ser9Gly) represents a non-synonymous point mutation, where serine is replaced by glycine (Ser9Gly), in position 9 of the N terminal part of the receptor. The Ser9Gly mutation affects the extracellular N-terminus of the DRD3, which does not appear to participate in receptor ligand binding [57], a possible explanation for the lack of reproducibility of positive associations between the Ser9Gly *DRD3* variant and ET.

The rs6280, was considered a candidate genetic risk factor for ET because it is mapped in chromosome 3q13, in the ETM1 locus [58], a locus that emerged through a genome wide linkage scan in Icelandic families (ETM1; OMIM: 190300) [59]. Indeed, the linkage peak markers of the ETM1 locus, namely D3S1278 and D3S1267, are located 1 and 10 Mb far from the *DRD3* gene, respectively [59]. Another reason for the *DRD3* appropriateness as a candidate genetic risk factor for ET, was the fact that *DRD3* has been previously associated with tardive dyskinesia, phenotypic appearance of Parkinson's Disease (PD), and with its expression reported decreased in patients with PD [60–63].

Following this train of thought, in 2006, Jeanneteau et al., reported that rs6280 was associated with risk and age at onset of ET in a Caucasian population [63] while positive associations were also found in a French sample [57]. The latest case-control study involved a Spanish population, where rs6280 was associated with risk and age at onset of ET, as well as with the risk for voice tremor [58]. Despite the robustness of the results even after a pooled meta-analysis, the magnitude of the association remained weak, suggesting that the association between rs6280 and ET may represent a false positive observation [58], and that rs6280 does not represent a strong risk factor for ET. The latter could partly explain the lack of replication of the association between this marker and ET in Latvian, Russian, Belarusians, Ukrainians, Polish, Lithuanians [64], Asians [65], Italians [66], Germans, Danish, French [67], and overall Caucasians [68].

Apart from the ETM1 locus, ETM2 (OMIM: 602134) [69] and ETM3 (OMIM: 611456) [70] have also been considered as causal genetic factors for ET in a genome wide linkage

scan, without though, as in case of ETM1 locus, the genes and the causal mutations for both, ETM2 and ETM3, loci being identified [3]. Inashkina et al. performed CGAS genotyping short tandem repeat (STR) markers located within ETM1 and ETM2 loci in Latvian patients with ET, and the biggest differentiation of frequencies was found for allele 171 of the marker D2S220 (OR 0.13, 95% CI 0.02–1.03, P = 0.05) [64]. Zahorakova et al. performed a genetic analysis of three polymorphic loci (etm1231, etm1234, and etm1240) located within the ETM2 candidate region in 61 Czech patients with a family history of ET and 68 healthy controls, but the allele frequencies did not significantly differ between cases and controls [71]. Therefore, the importance of these polymorphisms is still hard to assess, as they have yet to make an appearance in other studies.

## 5. ALAD (d-aminolevulinic acid dehydratase), VDR (Vitamin D Receptor), HMOX1 (heme oxygenase 1) and HMOX2 (heme oxygenase 2)

The d-aminolevulinic acid dehydratase (ALAD) catalyzes the second step in heme synthesis, leading to the production of cobalamin-monopyrrole-porphobilinogen [72, 73], and the *ALAD* gene has been shown to influence the toxicokinetics of lead [74]. *ALAD* gene has one polymorphism, giving way to two codominant alleles, ALAD-1 and ALAD-2 [74]. The non-synonymous coding variant rs1800435 (also known as K59N and G177C), creates the ALAD-2 variant allele [72] and carriers of the ALAD-2 variant may be more susceptible to lead toxicity [74]. To sum up, the *ALAD* gene may influence heme synthesis and lead toxicity. This is of interest in the context of ET, because lead intoxication produces a syndrome involving tremor and lead has been named an environmental susceptibility factor for ET [75].

The *vitamin D receptor (VDR)* gene, encodes the vitamin D receptor, and it seems that genetic variability of *VDR* may also affect lead toxicity [73]. On the other hand, the heme oxygenase (HMOX) enzyme is also involved in heme catabolism. There are two isozymes, the inducible heme oxygenase-1 (HMOX1) and the constitutive heme oxygenase-2 (HMOX2), encoded by the *HMOX1* and *HMOX2* genes respectively [76]. As ET and PD share many features, and variants across *VDR*, *HMOX1*, and *HMOX2* genes have been reported to confer susceptibility to PD [77, 78], and as lead exposure has been associated with PD [79], it was reasonable that variants across these genes could be targets for CGASs regarding ET.

Regarding the *ALAD* gene, the odds of ET were increased in individuals who carried an ALAD-2 allele and had an elevated blood lead concentration, when compared to individuals with only elevated blood lead concentration [74]. In a study in Caucasian Spanish, the *ALAD* rs1800435 polymorphism was not associated with familial essential tremor (FET) risk, but its interaction with the *HMOX2* rs1051308 polymorphism could be weakly associated with the FET [80]. *HMOX1* (rs2071746) and *HMOX2* (rs4786504, rs1051308) did not associate with ET in the Chinese [18], while the

allelic frequencies of rs2071746T (OR = 0.76, p = 0.015) and rs1051308G (OR = 0.71, p = 0.004) were lower in Spanish white ET patients [76].

Regarding the *VDR* gene, the TT genotype of the rs2228570 was associated with sporadic essential tremor (SET) (p = 0.033; OR = 0.453 and similarly, the C allele was associated with an increased risk of SET (p = 0.033; OR = 2.207) [81], while the rs731236 did not associate with ET in Chinese [18].

## 6. LRRK2 (Leucine-rich repeat kinase 2), LRRK1 (Leucine-rich repeat kinase 1), SNCA (non A4 component of amyloid precursor/Alpha-synuclein), GBA (Glucocerebrosidase) and MAPT (microtubule-associated protein tau)

A number of PD/parkinsonism related genes [*Leucine-rich repeat kinase 2 (LRRK2), Alpha-synuclein (SNCA), Glucocerebrosidase (GBA), microtubule-associated protein tau (MAPT)*] have been examined for possible association with ET. LRRK2 is a large multi-domain protein kinase, mainly localized in the cytoplasm [82]. Pathogenic variants of *LRRK2*, may lead to elevated LRRK2 kinase activity, which appears to mediate neuronal toxicity [82] and mutations across the *LRRK2* gene have also been incriminated for familial PD [83]. Moreover, the phenotypic appearance of PD patients with mutations on LRRK2 could be initially resembled to ET phenotype [84]. Due to all these, LRRK2 has been included as a target in ET CGASs. The *leucine-rich repeat kinase 1 (LRRK1)* gene is a paralog of LRRK2, while many variants have been linked to PD as well [85]. The *LRRK2* R1628P variant has previously been associated with ET. More precisely, carriers of R1628P appeared to have a two-fold increased risk of ET (p = 0.0035, OR = 2.20) in a cohort consisting mainly of Asians (90%) [86]. However, other examined variants of *LRRK1* and *LRRK2* genes, in Asian and Non-Hispanic whites cohorts [84, 87–89], failed to present any association with ET.

SNCA constitutes the main component of Lewy bodies, neurites and glial cytoplasmic inclusions, which are considered as the key pathological feature in PD and multiple system atrophy (MSA) [90]. The NACP-Rep1 polymorphism is located in the promoter region of the *SNCA* gene [90–92]. Variants in this locus of *SNCA* have been shown to be implicated in the regulation of the *SNCA* gene expression [90] and the 263bp allele of the NACP-Rep1 was encountered more frequently in ET patients than healthy controls [90]. However, two additional studies regarding *SNCA* variability association and ET failed to provide any association [91, 92].

The *GBA* gene encodes the enzyme glucocerebrosidase, which is the causative gene for Gaucher disease, a lysosomal storage disease with an autosomal recessive mode of inheritance [93]. The L444P mutation of the *GBA* gene represents the commonest pathogenic mutation for Gaucher disease in China [94]. While the N370S, R496H, E326K and the R44C mutations have been identified in ET cases [89], studies so far, regarding ET and *GBA*, have not provided evidence that the *GBA* gene is a major risk factor for ET [89, 95].

Mutations in the *MAPT* gene cause frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP- 17), and additionally, the H1 haplotype of *MAPT* gene has been associated with increased risk for disorders with a-synuclein pathology [96–98]. Three studies have been so far conducted concerning ET and variants across the *MAPT* gene [99–101], but only MAPT H1 was associated with ET, among North American Caucasians [99].

## 7. FUS/TLS (Fused in sarcoma/Translated in liposarcoma)

Pathogenic mutations in *Fused in sarcoma/Translated in liposarcoma (FUS/TLS)* are causing factors for amyotrophic lateral sclerosis (ALS) (4% of familial cases and <1% of sporadic ALS cases) [73, 102] and frontotemporal lobar degeneration (FTLD) [103].

Merner et al. detected the p.Arg216Cys variant in two ET cases (one familial and one sporadic), and the p.Pro431Leu in a case with familial ET [104]. The non-pathogenic mutation p.G174_G175del in one ET patient and two healthy controls, and a novel p.R377W in one patient that had positive family history of disease, were also identified [105]. Moreover, the Met392Ile in the FUS gene has been reported to increase susceptibility to ET among a Chinese sample [106]. Ortega-Cubero et al., detected a few *FUS* gene variants in a Spanish cohort, none of them found associated with ET, however, when compared to controls from the 1000 Genomes project [107]. Finally, three other studies reported negative results [108–110]. Therefore, the bibliographic data lead us to believe that rare variants across the *FUS* gene may compromise a rare cause of monogenic ET [111].

## 8. CYPs (Cytochromes P450) genes

Cytochromes P450 (CYPs) consist a large family of enzymes that oxidize steroids, fatty acids, xenobiotics, drugs, pesticides, and heavy metals, mainly aiming to the clear the organism from various compounds, while also participating in hormone synthesis and breakdown [112]. The human CYP superfamily contains over 100 functional genes and pseudogenes, while *CYP* genetic variability appears to have an effect to the risk of various diseases and to pharmacogenetics [113, 114].

Primidone is a drug that appears to be effective, to some degree, in the management of ET [115]. Primidone is partly metabolized by CYP2C19 [113]. Homozygotes for the defective alleles are considered as poor metabolizers, while carriers of more functional alleles as extensive metabolizers [114]. Heterozygosis for CYP2C19*1/CYP2C19*2 has been associated with the risk for ET in Caucasians [114] and genetic alternations in *CYP2C8* and *CYP2C9* genes (which are in high genetic linkage with the *CYP2C19* gene, especially among Caucasians) [116], have further been associated with the risk for ET [114, 116].

The *CYP2D6* (Cytochrome P450 2D6) gene appears to have the largest phenotypical variability among the *CYP* genes [117]. Genetic status regarding *CYP2D6* gene affects the metabolism of the debrisoquine, as carriers of defect alleles poorly metabolize debrisoquine, in contrast to the effective metabolizers, who carry functional alleles [117]. As the *CYP2D6* gene has been associated with PD, Agunez et al. genotyped 91 ET patients and 258 controls for 8 *CYP2D6* variants, but failed to detect any association [118].

## 9. Other genes

Polymorphisms in genes associated with Restless legs syndrome (RLS) [rs8193036 of *interleukin-17A gene (IL17A)*, rs1143643, rs1143634, and rs1143633 of *interleukin-1B (IL1B)* gene, rs693534 and rs7977109 of *nitric oxide synthase 1 (NOS1)* gene and rs6413413 and rs1229984 of *alcohol dehydrogenase (ADH1B)* gene] have been examined for possible association with ET [18]. Solely rs1143633 of *IL1B* was associated with the risk of ET after adjusting for age and gender (recessive model) and after multiple comparisons correction (OR = 2.63, p = 0.002) [18].

The Triggering Receptor Expressed on Myeloid cells 2 (TREM2), coded by the *TREM2* gene [119], is a transmembrane signaling protein, pairing up with Tyrosine Kinase-binding protein (TYROBP/DP12), and is involved in innate immune system functions such as inflammation, proliferation and phagocytosis [120]. The R47H (rs75392628) is the most extensively studied genetic variant across the *TREM2* gene, which results in reduced signaling, lipoprotein uptake and binding, and surface uptake [120, 121]. The rs75392628 has been associated with Alzheimer's disease, sporadic ALS, the logopenic variant of primary progressive aphasia, and frontotemporal dementia- behavioral variant [121]. In 2015, based on the neurodegenerative hypothesis, Ortega-Cubero et al. found an association between rs75392628 and ET in a Spanish population (OR = 5.97, p = 0.042), without replication though [122].

Another variant that has been associated with ET is rs12456492 of another PD related gene, the *Ras-like without CAAX 2 (RIT2)* [123]. Additionally, the homozygosity for the missense variant (rs11558538) 105Thr genotype of the *Histamine N-Methyltransferase (HNMT)* gene was found to be more frequent in Caucasian Spanish ET patients [124], but not in Caucasian ET patients from North America [125]. The 677T, 1298C alleles, the T677T and T677T/A1298A genotypes, and the C677C/C1298C compound genotypes of *methylenetetrahydrofolate reductase (MTHFR)* gene [126], were also associated with ET [127]. Finally, the proportion of subjects carrying rare short (CAG)5–7 alleles of the *Protein Phosphatase 2 Regulatory Subunit Bbeta (PPP2R2B)* gene was higher in an ET patient cohort [4/132 (3.0%), p < 0.001] when compared to controls [1/625 [(0.2%)] [128].

Moving on, the rs1695 of the *Glutathione S-Transferase Pi 1 (GSTP1)* gene was significantly more frequently encountered in individuals with ET exposed to pesticides when compared to non-exposed patients [129]. The non-synonymous functional coding variants rs662 (Q192R) and the rs854560 (L55M) of *paraoxonase-1 (PON1)* gene [130], [which encode the homonymous serum calcium

dependent esterase enzyme which mainly hydrolyze the active metabolites (oxons) of some organophosphate pesticides such as diazinon, parathion and chlorpyrifos)] [131], have not been associated with ET. Negative association studies between ET and gamma-aminobutyric acid A receptors (GABRA) [132–134], *gamma-aminobutyric acid receptor rho* genes [*GABRR1, GABRR2,* and *GABRR3*] [135], and *GABA transporter* genes [133], and the a A265G variant in the *HS1 binding protein 3 (HS1BP3)* gene [136], (a gene that had been previously found in families with ET [137]). Finally, there is no indication that the *alcohol dehydrogenase 2 (ADH2)* [138], the *human small conductance calcium-activated potassium channel (hSKCa3)* and the *calcium voltage-gated channel subunit alpha1 A (CACNL1A4)* genes rank among the ET genetic risk factors [139].

## Meta-analyses

There was no indication of publication bias (p > 0.10 for Egger's test). A marginal association was observed for the *STK32B* rs10937625 (fixed model OR: 0.80; 95%CI: 0.65–0.99, pz = 0.04) [27, 28]. The results of the meta-analyses (number of included studies, $I^2$, $P_Q$, applied model, OR, 95% CI, p-value) regarding *LINGO1* rs9652490, *LINGO1* rs11856808, *SLC1A2* rs3794087, *STK32B* rs10937625 and *PPARGC1A* rs17590046 are summarized in **Table 2**. Forest plots for the overall analysis are depicted in **Figure 2**. In the sensitivity analysis the pooled ORs (95% CIs) ranged from 1.04 (95% CI: 0.95–1.14) to 1.16 (95% CI: 0.99–1.36). After omitting each study one at a time for the LINGO1 rs9652490, a marginal trend for association was revealed when either the study of Lorenzo-Betancor [34] (random model OR: 1.16; 95%CI: 0.99-1.35, pz = 0.06) or the one of Vilarino-Guell [28] (random model OR: 1.16; 95%CI: 0.99–1.36, pz = 0.06) was omitted. Results from sensitivity analyses are presented at **Table 3**, while the forest plots are accessible at Supporting File 3.

A few meta-analyses concerning the role of genetic variants at ET have been conducted [34, 50, 58, 140–143]. Regarding *LINGO1* rs9652490 and *LINGO1* rs11856808, previous meta-analyses have reported association with ET [34, 141, 142]. The lack of the association in our meta-analysis it may be due the fact that we did not include data (neither from the discovery phase nor from the follow-up) from the GWAS from Stefansson et al. [19]. It also could be attributed to the high heterogeneity ($I^2$ = 58%, $P_Q$ = 0.01) that was observed in the current meta-analysis. For the *SLC1A2* rs3794087 our results are in accordance with previous meta-analyses [50, 140, 142], that failed to report any association, despite the fact that we did not used the GWAS from Their et al., [20] and we also include data from Ross et al. [54]. Finally, the marginal association between *STK32B* rs10937625 and ET should be interpreted with caution as the analysis based on only two studies in Asian populations.

## Conclusions

In the current review, we thoroughly reviewed 74 articles regarding genes and genetic loci that confer susceptibility to ET. Based on our results, over 50 genes/genetic loci have been examined for possible association with ET. Results from our meta-analyses suggest that LINGO1 rs9652490 and STK32B rs10937625 may influence, to some extent, ET susceptibility. However, despite the considerable number of studies that have been conducted and the significant effort made in order to identify genes of ET, consistently repeated results have yet to appear.. These could be attributed, to some extent, to diagnostic difficulties (as the diagnosis is based on clinical evaluation) [144–150], heterogeneity among ancestry in studies, ethnicity, variability of the power of the sample sizes, different statistical and methodological approaches among studies, and other confounding factors.

Our study has some limitations. Firstly, we included studies without performing any quality assessment, in order

**Table 2:** Results from meta-analyses of the LINGO1 rs9652490, LINGO1 rs11856808, SLC1A2 rs3794087, STK32B rs10937625 and PPARGC1A rs17590046 for association with ET.

| Gene | Polymorphism | Number of studies[Ref.] | Population | Heterogeneity | | Meta-analysis model | Test for overall effect | |
|------|--------------|-------------------------|------------|------|------|------|------|------|
| | | | | $I^2$ | $P_Q$ | | OR (95% CI) | P-value |
| LINGO1 | rs9652490 | 10 [28, 31, 33–35, 37–40] | Mixed | 58% | 0.01 | Random | 1.12 (0.97–1.30) | 0.11 |
| LINGO1 | rs11856808 | 7 [31, 34, 35, 38–40] | Mixed | 53% | 0.05 | Random | 1.06 (0.91–1.24) | 0.43 |
| SLC1A2 | rs3794087 | 6 [50–54] | Mixed | 67% | 0.01 | Random | 0.95 (0.77–1.16) | 0.60 |
| STK32B | rs10937625 | 2 [55, 56] | Asian | 61% | 0.11 | Fixed | 0.80 (0.65–0.99) | 0.04 |
| PPARGC1A | rs17590046 | 2 [55, 56] | Asian | 59% | 0.12 | Fixed | 0.79 (0.61–1.03) | 0.09 |

ET, essential tremor; LINGO1, leucine-rich repeat and lg domain containing nogo receptor-interacting protein 1; SLC1A2, solute carrier family 1 member 2; PPARGC1A, Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha; RIT2, Ras like without CAAX 2; STK32B, serine/threonine kinase 32B; OR, odds ratio; CI, confidence interval.
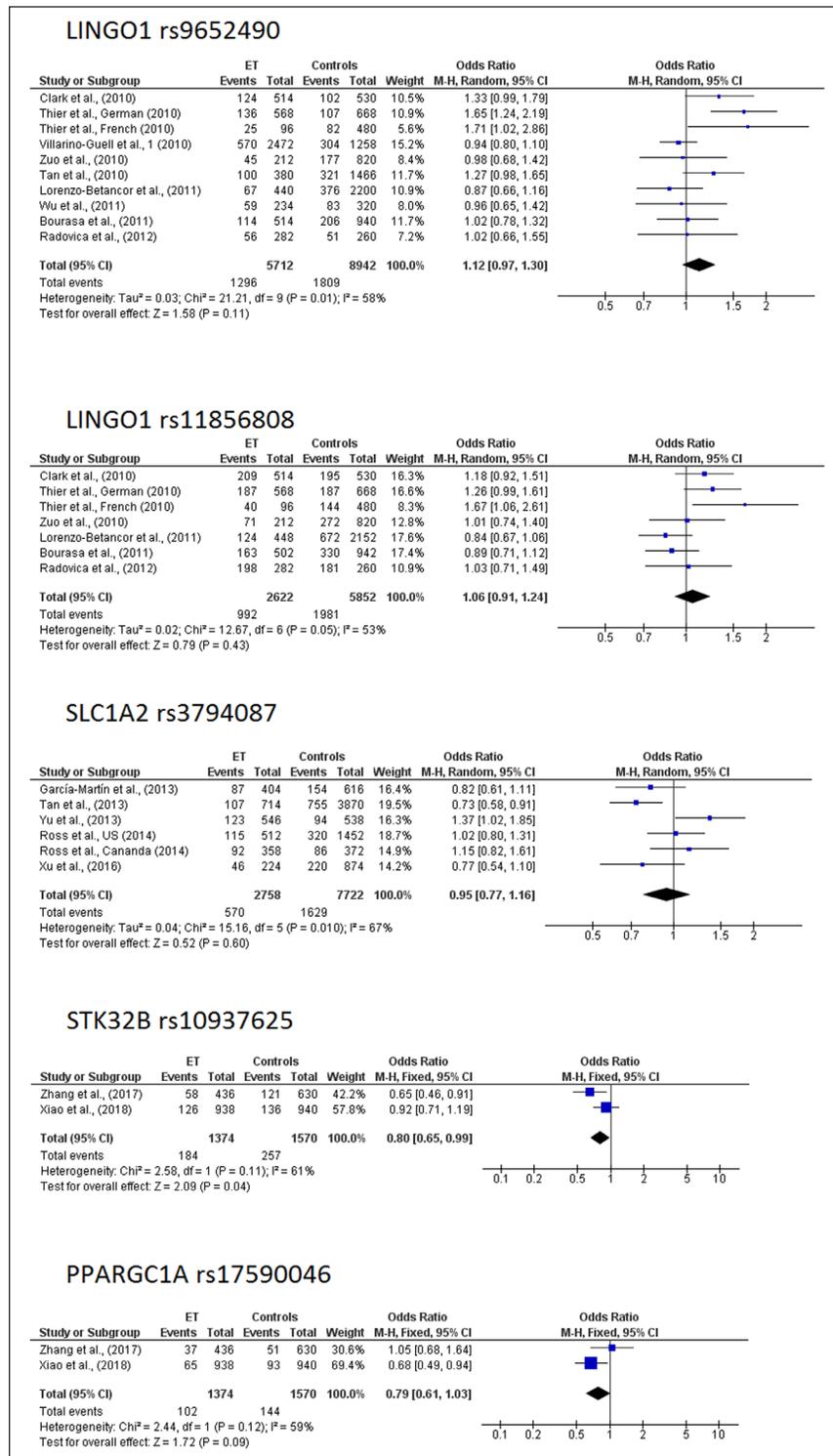
**Figure 2:** Forest Plots presenting the results from meta-analyses.

to present the most accurate data possible. Moreover, the possibility that some eligible studies failed to be obtained through our search strategy is unlikely but cannot completely be excluded. Finally, the current review would have more robustness if more family, twin and whole exome studies regarding ET had included.

In view of the former considerations, collaborative studies with adjustment for other possible ET confounders (e.g. consumption of b-carboline alkaloid, caffeine and ethanol, harmane, exposure to pesticides, lead and other heavy metals, antioxidants, smoking and aging among others) are needed. In this way, the pathophysiological mechanisms of

**Table 3:** Results from the sensitivity meta-analyses of the LINGO1 rs9652490 for association with ET.

| Omitted study | Heterogeneity | | Meta-analysis model | Test for overall effect | |
|---|---|---|---|---|---|
| | I² | $P_Q$ | | OR (95% CI) | P-value |
| Clark et al., (2010) [31] | 58% | 0.01 | Random | 1.10 (0.94–1.29) | 0.22 |
| Thier et al., German (2010) [40] | 33% | 0.15 | Fixed | 1.04 (0.95–1.14) | 0.43 |
| Thier et al., French (2010) [40] | 56% | 0.02 | Random | 1.10 (0.95–1.26) | 0.21 |
| Villarino-Guell et al., 2 (2010) [28] | 52% | 0.04 | Random | 1.16 (0.99–1.36) | 0.06 |
| Zuo et al., (2010) [35] | 62% | 0.007 | Random | 1.14 (0.97–1.33) | 0.10 |
| Tan et al., (2010) [33] | 59% | 0.01 | Random | 1.11 (0.94–1.30) | 0.21 |
| Lorenzo-Betancor et al., (2011) [34] | 57% | 0.02 | Random | 1.16 (0.99–1.35) | 0.06 |
| Wu et al., (2011) [37] | 62% | 0.008 | Random | 1.14 (0.98–1.33) | 0.10 |
| Bourasa et al., (2011) [39] | 62% | 0.007 | Random | 1.14 (0.97–1.34) | 0.11 |
| Radovica et al., (2011) [38] | 62% | 0.007 | Random | 1.13 (0.97–1.33) | 0.11 |

ET, essential tremor; LINGO1, leucine-rich repeat and lg domain containing nogo receptor-interacting protein 1; OR, odds ratio; CI, confidence interval.

ET and the net effect of the genetic and environmental contribution to this entity could be revealed.

## Additional Files
The additional files for this article can be found as follows:

- **Supporting File 1.** The complete search algorithm. DOI: https://doi.org/10.5334/tohm.67.s1
- **Supporting File 2.** Baseline characteristics from the studies. DOI: https://doi.org/10.5334/tohm.67.s2
- **Supporting File 3.** Forest plots from sensitivity analyses. DOI: https://doi.org/10.5334/tohm.67.s3

## Competing Interests
The authors have no competing interests to declare.

## References

1. **Jankovic J.** Essential tremor: a heterogenous disorder. *Movement disorders: official journal of the Movement Disorder Society.* 2002;17(4): 638–44. DOI: https://doi.org/10.1002/mds.10221
2. **Louis ED.** The primary type of tremor in essential tremor is kinetic rather than postural: cross-sectional observation of tremor phenomenology in 369 cases. *European journal of neurology.* 2013; 20(4): 725–7. DOI: https://doi.org/10.1111/j.1468-1331.2012.03855.x
3. **Clark LN, Louis ED.** Essential tremor. *Handbook of clinical neurology.* 2018; 147: 229–39. DOI: https://doi.org/10.1016/B978-0-444-63233-3.00015-4
4. **Louis ED, Benito-Leon J, Bermejo-Pareja F.** Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. *European journal of neurology.* 2007; 14(10): 1138–46. DOI: https://doi.org/10.1111/j.1468-1331.2007.01923.x
5. **Bermejo-Pareja F, Puertas-Martin V.** Cognitive features of essential tremor: a review of the clinical aspects and possible mechanistic underpinnings. *Tremor and other hyperkinetic movements (New York, NY).* 2012; 2.
6. **Espay AJ, Lang AE, Erro R, Merola A, Fasano A, Berardelli A,** et al. Essential pitfalls in "essential" tremor. *Movement disorders: official journal of the Movement Disorder Society.* 2017; 32(3): 325–31. DOI: https://doi.org/10.1002/mds.26919
7. **Zdrodowska MA, Cersonsky TEK, Salardini A, Cosentino S, Louis ED.** Dementia in Essential Tremor: A Visual Record. *Tremor and other hyperkinetic movements (New York, NY).* 2019; 9: 635.
8. **Barbosa R, Mendonca M, Ladeira F, Miguel R, Bugalho P.** Probable REM-Sleep Behavior Disorder and Dysautonomic Symptoms in Essential Tremor. *Tremor and other hyperkinetic movements (New York, NY).* 2017; 7: 522.
9. **Louis ED, Dure LS, Pullman S.** Essential tremor in childhood: a series of nineteen cases. *Movement disorders: official journal of the Movement Disorder Society.* 2001; 16(5): 921–3. DOI: https://doi.org/10.1002/mds.1182
10. **Jimenez-Jimenez FJ, de Toledo-Heras M, Alonso-Navarro H, Ayuso-Peralta L, Arevalo-Serrano J, Ballesteros-Barranco A,** et al. Environmental risk factors for essential tremor. *European neurology.* 2007; 58(2): 106–13. DOI: https://doi.org/10.1159/000103646
11. **Ong YL, Deng X, Tan EK.** Etiologic links between environmental and lifestyle factors and Essential tremor. *Annals of clinical and translational neurology.* 2019; 6(5): 979–89. DOI: https://doi.org/10.1002/acn3.758

12. **Louis ED, Hernandez N, Rabinowitz D, Ottman R, Clark LN.** Predicting age of onset in familial essential tremor: how much does age of onset run in families? *Neuroepidemiology.* 2013; 40(4): 269–73. DOI: https://doi.org/10.1159/000345253

13. **Louis ED.** Environmental epidemiology of essential tremor. *Neuroepidemiology.* 2008; 31(3): 139–49. DOI: https://doi.org/10.1159/000151523

14. **Revuelta G, McGill C, Jensen JH, Bonilha L.** Characterizing Thalamo-Cortical Structural Connectivity in Essential Tremor with Diffusional Kurtosis Imaging Tractography. *Tremor and other hyperkinetic movements (New York, NY).* 2019; 9.

15. **Jimenez-Jimenez FJ, Garcia-Martin E, Alonso-Navarro H, Lorenzo-Betancor O, Ortega-Cubero S, Pastor P,** et al. A family study of *DRD3* rs6280, *SLC1A2* rs3794087 and *MAPT* rs1052553 variants in essential tremor. *Neurological research.* 2016; 38(10): 880–7. DOI: https://doi.org/10.1080/01616412.2016.1210355

16. **Naranjo KV, Park J, Chen KP, Hernandez N, Clark LN, Ottman R,** et al. Genetic Testing Preferences of Individuals in Families with Essential Tremor. *Tremor and other hyperkinetic movements (New York, NY).* 2018; 8: 545.

17. **Tanner CM, Goldman SM, Lyons KE, Aston DA, Tetrud JW, Welsh MD,** et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. *Neurology.* 2001; 57(8): 1389–91. DOI: https://doi.org/10.1212/WNL.57.8.1389

18. **Chen J, Huang P, He Y, Shen J, Du J, Cui S,** et al. *IL1B* polymorphism is associated with essential tremor in Chinese population. *BMC neurology.* 2019; 19(1): 99. DOI: https://doi.org/10.1186/s12883-019-1331-5

19. **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. *Nature genetics.* 2009; 41(3): 277–9. DOI: https://doi.org/10.1038/ng.299

20. **Thier S, Lorenz D, Nothnagel M, Poremba C, Papengut F, Appenzeller S,** et al. Polymorphisms in the glial glutamate transporter *SLC1A2* are associated with essential tremor. *Neurology.* 2012; 79(3): 243–8. DOI: https://doi.org/10.1212/WNL.0b013e31825fdeed

21. **Muller SH, Girard SL, Hopfner F, Merner ND, Bourassa CV, Lorenz D,** et al. Genome-wide association study in essential tremor identifies three new loci. *Brain: a journal of neurology.* 2016; 139(Pt 12): 3163–9. DOI: https://doi.org/10.1093/brain/aww242

22. **DerSimonian R, Laird N.** Meta-analysis in clinical trials. *Controlled clinical trials.* 1986; 7(3): 177–88. DOI: https://doi.org/10.1016/0197-2456(86)90046-2

23. **Siokas V, Dardiotis E, Tsironi EE, Tsivgoulis G, Rikos D, Sokratous M,** et al. The Role of TOR1A Polymorphisms in Dystonia: A Systematic Review and Meta-Analysis. *PloS one.* 2017; 12(1): e0169934. DOI: https://doi.org/10.1371/journal.pone.0169934

24. **Siokas V, Kardaras D, Aloizou AM, Asproudis I, Boboridis KG, Papageorgiou E,** et al. BDNF rs6265 (Val66Met) Polymorphism as a Risk Factor for Blepharospasm. *Neuromolecular medicine.* 2019; 21(1): 68–74. DOI: https://doi.org/10.1007/s12017-018-8519-5

25. **Mantel N, Haenszel W.** Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute.* 1959; 22(4): 719–48.

26. **Egger M, Davey Smith G, Schneider M, Minder C.** Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical research ed).* 1997; 315(7109): 629–34. DOI: https://doi.org/10.1136/bmj.315.7109.629

27. **Vilarino-Guell C, Ross OA, Wider C, Jasinska-Myga B, Cobb SA, Soto-Ortolaza AI,** et al. LINGO1 rs9652490 is associated with essential tremor and Parkinson disease. *Parkinsonism & related disorders.* 2010; 16(2): 109–11. DOI: https://doi.org/10.1016/j.parkreldis.2009.08.006

28. **Vilarino-Guell C, Wider C, Ross OA, Jasinska-Myga B, Kachergus J, Cobb SA,** et al. LINGO1 and LINGO2 variants are associated with essential tremor and Parkinson disease. *Neurogenetics.* 2010; 11(4): 401–8. DOI: https://doi.org/10.1007/s10048-010-0241-x

29. **Mi S, Sandrock A, Miller RH.** LINGO-1 and its role in CNS repair. *The international journal of biochemistry & cell biology.* 2008; 40(10): 1971–8. DOI: https://doi.org/10.1016/j.biocel.2008.03.018

30. **Zhao XH, Jin WL, Wu J, Mi S, Ju G.** Inactivation of glycogen synthase kinase-3beta and up-regulation of LINGO-1 are involved in LINGO-1 antagonist regulated survival of cerebellar granular neurons. *Cellular and molecular neurobiology.* 2008; 28(5): 727–35. DOI: https://doi.org/10.1007/s10571-007-9258-6

31. **Clark LN, Park N, Kisselev S, Rios E, Lee JH, Louis ED.** Replication of the LINGO1 gene association with essential tremor in a North American population. *European journal of human genetics: EJHG.* 2010; 18(7): 838–43. DOI: https://doi.org/10.1038/ejhg.2010.27

32. **Louis ED, Yi H, Erickson-Davis C, Vonsattel JP, Faust PL.** Structural study of Purkinje cell axonal torpedoes in essential tremor. *Neuroscience letters.* 2009; 450(3): 287–91. DOI: https://doi.org/10.1016/j.neulet.2008.11.043

33. **Tan EK, Teo YY, Prakash KM, Li R, Lim HQ, Angeles D,** et al. LINGO1 variant increases risk of familial essential tremor. *Neurology.* 2009; 73(14): 1161–2. DOI: https://doi.org/10.1212/WNL.0b013e3181bacfc9

34. **Lorenzo-Betancor O, Garcia-Martin E, Cervantes S, Agundez JA, Jimenez-Jimenez FJ, Alonso-Navarro H,** et al. Lack of association of LINGO1 rs9652490 and rs11856808 SNPs with

familial essential tremor. *European journal of neurology*. 2011; 18(8): 1085–9. DOI: https://doi.org/10.1111/j.1468-1331.2010.03251.x

35. **Zuo X, Jiang H, Guo JF, Yu RH, Sun QY, Hu L,** et al. Screening for two SNPs of LINGO1 gene in patients with essential tremor or sporadic Parkinson's disease in Chinese population. *Neuroscience letters*. 2010; 481(2): 69–72. DOI: https://doi.org/10.1016/j.neulet.2010.06.041

36. **Liang H, Song Z, Deng X, Xu H, Zhu A, Zheng W,** et al. Genetic analysis of the leucine-rich repeat and Ig domain containing Nogo receptor-interacting protein 1 gene in essential tremor. *Journal of molecular neuroscience: MN*. 2013; 51(2): 403–7. DOI: https://doi.org/10.1007/s12031-013-0029-1

37. **Wu YW, Rong TY, Li HH, Xiao Q, Fei QZ, Tan EK,** et al. Analysis of Lingo1 variant in sporadic and familial essential tremor among Asians. *Acta neurologica Scandinavica*. 2011; 124(4): 264–8. DOI: https://doi.org/10.1111/j.1600-0404.2010.01466.x

38. **Radovica I, Inashkina I, Smeltere L, Vitols E, Jankevics E.** Screening of 10 SNPs of LINGO1 gene in patients with essential tremor in the Latvian population. *Parkinsonism & related disorders*. 2012; 18(1): 93–5. DOI: https://doi.org/10.1016/j.parkreldis.2011.06.006

39. **Bourassa CV, Riviere JB, Dion PA, Bernard G, Diab S, Panisset M,** et al. LINGO1 variants in the French-Canadian population. *PloS one*. 2011; 6(1): e16254. DOI: https://doi.org/10.1371/journal.pone.0016254

40. **Thier S, Lorenz D, Nothnagel M, Stevanin G, Durr A, Nebel A,** et al. LINGO1 polymorphisms are associated with essential tremor in Europeans. *Movement disorders: official journal of the Movement Disorder Society*. 2010; 25(6): 717–23. DOI: https://doi.org/10.1002/mds.22887

41. **Wu YW, Prakash KM, Rong TY, Li HH, Xiao Q, Tan LC,** et al. Lingo2 variants associated with essential tremor and Parkinson's disease. *Human genetics*. 2011; 129(6): 611–5. DOI: https://doi.org/10.1007/s00439-011-0955-3

42. **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 expression patterns: GEP*. 2009; 9(1): 1–26. DOI: https://doi.org/10.1016/j.gep.2008.09.004

43. **Haines BP, Rigby PW.** Expression of the Lingo/LERN gene family during mouse embryogenesis. *Gene expression patterns: GEP*. 2008; 8(2): 79–86. DOI: https://doi.org/10.1016/j.modgep.2007.10.003

44. **Liang H, Zheng W, Xu H, Lei J, Song Z, Jiang X,** et al. No evidence of association between the LINGO4 gene and essential tremor in Chinese Han patients. *Parkinsonism & related disorders*. 2012; 18(3): 303–5. DOI: https://doi.org/10.1016/j.parkreldis.2011.10.017

45. **Siokas V, Fotiadou A, Dardiotis E, Kotoula MG, Tachmitzi SV, Chatzoulis DZ,** et al. SLC2A1 Tag SNPs in Greek Patients with Diabetic Retinopathy and Nephropathy. *Ophthalmic research*. 2019; 61(1): 26–35. DOI: https://doi.org/10.1159/000480241

46. **Kim K, Lee SG, Kegelman TP, Su ZZ, Das SK, Dash R,** et al. Role of excitatory amino acid transporter-2 (EAAT2) and glutamate in neurodegeneration: opportunities for developing novel therapeutics. *Journal of cellular physiology*. 2011; 226(10): 2484–93. DOI: https://doi.org/10.1002/jcp.22609

47. **Berger UV, Hediger MA.** Comparative analysis of glutamate transporter expression in rat brain using differential double in situ hybridization. *Anatomy and embryology*. 1998; 198(1): 13–30. DOI: https://doi.org/10.1007/s004290050161

48. **Wu J, Lee MR, Choi S, Kim T, Choi DS.** ENT1 regulates ethanol-sensitive EAAT2 expression and function in astrocytes. *Alcoholism, clinical and experimental research*. 2010; 34(6): 1110–7. DOI: https://doi.org/10.1111/j.1530-0277.2010.01187.x

49. **Handforth A, Kadam PA, Kosoyan HP, Eslami P.** Suppression of Harmaline Tremor by Activation of an Extrasynaptic GABAA Receptor: Implications for Essential Tremor. *Tremor and other hyperkinetic movements (New York, NY)*. 2018; 8: 546.

50. **Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P,** et al. No association of the SLC1A2 rs3794087 allele with risk for essential tremor in the Spanish population. *Pharmacogenetics and genomics*. 2013; 23(11): 587–90. DOI: https://doi.org/10.1097/FPC.0b013e328364db9d

51. **Tan EK, Foo JN, Tan L, Au WL, Prakash KM, Ng E,** et al. SLC1A2 variant associated with essential tremor but not Parkinson disease in Chinese subjects. *Neurology*. 2013; 80(17): 1618–9. DOI: https://doi.org/10.1212/WNL.0b013e31828f1903

52. **Xu Y, Cao B, Chen Y, Ou R, Wei Q, Yang J,** et al. SLC1A2 rs3794087 are associated with susceptibility to Parkinson's disease, but not essential tremor, amyotrophic lateral sclerosis or multiple system atrophy in a Chinese population. *Journal of the neurological sciences*. 2016; 365: 96–100. DOI: https://doi.org/10.1016/j.jns.2016.04.003

53. **Yu SW, Chen CM, Chen YC, Chang CW, Chang HS, Lyu RK,** et al. SLC1A2 variant is associated with essential tremor in Taiwanese population. *PloS one*. 2013; 8(8): e71919. DOI: https://doi.org/10.1371/journal.pone.0071919

54. **Ross JP, Rayaprolu S, Bernales CQ, Soto-Ortolaza AI, van Gerpen J, Uitti RJ,** et al. SLC1A2 rs3794087 does not associate with essential tremor. *Neurobiology of aging*. 2014; 35(4): 935. e9–10. DOI: https://doi.org/10.1016/j.neurobiolaging.2013.09.022

55. **Zhang Y, Zhao Y, Zhou X, Li K, Yi M, Guo J,** et al. Assessment of Three New Loci from Genome-wide Association Study in Essential Tremor in Chinese

population. *Scientific reports.* 2017; 7(1): 7981. DOI: https://doi.org/10.1038/s41598-017-08863-5

56. **Xiao B, Deng X, Ng EY, Tio M, Prakash KM, Au WL,** et al. GWAS-linked PPARGC1A variant in Asian patients with essential tremor. *Brain: a journal of neurology.* 2017; 140(4): e24. DOI: https://doi.org/10.1093/brain/awx027

57. **Lucotte G, Lagarde JP, Funalot B, Sokoloff P.** Linkage with the Ser9Gly DRD3 polymorphism in essential tremor families. *Clinical genetics.* 2006; 69(5): 437–40. DOI: https://doi.org/10.1111/j.1399-0004.2006.00600.x

58. **Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Puertas I, Rubio L,** et al. Dopamine receptor D3 (DRD3) genotype and allelic variants and risk for essential tremor. *Movement disorders: official journal of the Movement Disorder Society.* 2009; 24(13): 1910–5. DOI: https://doi.org/10.1002/mds.22518

59. **Gulcher JR, Jonsson P, Kong A, Kristjansson K, Frigge ML, Karason A,** et al. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. *Nature genetics.* 1997; 17(1): 84–7. DOI: https://doi.org/10.1038/ng0997-84

60. **Ryoo HL, Pierrotti D, Joyce JN.** Dopamine D3 receptor is decreased and D2 receptor is elevated in the striatum of Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society.* 1998; 13(5): 788–97. DOI: https://doi.org/10.1002/mds.870130506

61. **Lerer B, Segman RH, Fangerau H, Daly AK, Basile VS, Cavallaro R,** et al. Pharmacogenetics of tardive dyskinesia: combined analysis of 780 patients supports association with dopamine D3 receptor gene Ser9Gly polymorphism. *Neuropsychopharmacology: official publication of the American College of Neuropsychopharmacology.* 2002; 27(1): 105–19. DOI: https://doi.org/10.1016/S0893-133X(02)00293-2

62. **Kusters CDJ, Paul KC, Guella I, Bronstein JM, Sinsheimer JS, Farrer MJ,** et al. Dopamine receptors and BDNF-haplotypes predict dyskinesia in Parkinson's disease. *Parkinsonism & related disorders.* 2018; 47: 39–44. DOI: https://doi.org/10.1016/j.parkreldis.2017.11.339

63. **Jeanneteau F, Funalot B, Jankovic J, Deng H, Lagarde JP, Lucotte G,** et al. A functional variant of the dopamine D3 receptor is associated with risk and age-at-onset of essential tremor. *Proceedings of the National Academy of Sciences of the United States of America.* 2006; 103(28): 10753–8. DOI: https://doi.org/10.1073/pnas.0508189103

64. **Inashkina I, Radovica I, Smeltere L, Vitols E, Jankevics E.** Case-control study of patients with essential tremor in Latvia. *European journal of neurology.* 2008; 15(9): 988–90. DOI: https://doi.org/10.1111/j.1468-1331.2008.02225.x

65. **Tan EK, Prakash KM, Fook-Chong S, Yih Y, Chua E, Lum SY,** et al. DRD3 variant and risk of essential tremor. *Neurology.* 2007; 68(10): 790–1. DOI: https://doi.org/10.1212/01.wnl.0000256773.87498.2f

66. **Vitale C, Gulli R, Ciotti P, Scaglione C, Bellone E, Avanzino L,** et al. DRD3 Ser9Gly variant is not associated with essential tremor in a series of Italian patients. *European journal of neurology.* 2008; 15(9): 985–7. DOI: https://doi.org/10.1111/j.1468-1331.2008.02164.x

67. **Lorenz D, Klebe S, Stevanin G, Thier S, Nebel A, Feingold J,** et al. Dopamine receptor D3 gene and essential tremor in large series of German, Danish and French patients. *European journal of human genetics: EJHG.* 2009; 17(6): 766–73. DOI: https://doi.org/10.1038/ejhg.2008.243

68. **Blair MA, Ma S, Phibbs F, Fang JY, Cooper MK, Davis TL,** et al. Reappraisal of the role of the DRD3 gene in essential tremor. *Parkinsonism & related disorders.* 2008; 14(6): 471–5. DOI: https://doi.org/10.1016/j.parkreldis.2007.11.002

69. **Higgins JJ, Pho LT, Nee LE.** A gene (ETM) for essential tremor maps to chromosome 2p22–p25. *Movement disorders: official journal of the Movement Disorder Society.* 1997; 12(6): 859–64. DOI: https://doi.org/10.1002/mds.870120605

70. **Shatunov A, Sambuughin N, Jankovic J, Elble R, Lee HS, Singleton AB,** et al. Genomewide scans in North American families reveal genetic linkage of essential tremor to a region on chromosome 6p23. *Brain: a journal of neurology.* 2006; 129(Pt 9): 2318–31. DOI: https://doi.org/10.1093/brain/awl120

71. **Zahorakova D, Ulmanova O, Kemlink D, Kofrankova M, Roth J, Martasek P,** et al. No association with the ETM2 locus in Czech patients with familial essential tremor. *Neuro endocrinology letters.* 2010; 31(4): 549–52.

72. **Wetmur JG.** Influence of the common human delta-aminolevulinate dehydratase polymorphism on lead body burden. *Environmental health perspectives.* 1994; 102(Suppl 3): 215–9. DOI: https://doi.org/10.1289/ehp.94102s3215

73. **Dardiotis E, Siokas V, Sokratous M, Tsouris Z, Michalopoulou A, Andravizou A,** et al. Genetic polymorphisms in amyotrophic lateral sclerosis: Evidence for implication in detoxification pathways of environmental toxicants. *Environment international.* 2018; 116: 122–35. DOI: https://doi.org/10.1016/j.envint.2018.04.008

74. **Louis ED, Applegate L, Graziano JH, Parides M, Slavkovich V, Bhat HK.** Interaction between blood lead concentration and delta-amino-levulinic acid dehydratase gene polymorphisms increases the odds of essential tremor. *Movement disorders: official journal of the Movement Disorder Society.* 2005; 20(9): 1170–7. DOI: https://doi.org/10.1002/mds.20565

75. **Dogu O, Louis ED, Tamer L, Unal O, Yilmaz A, Kaleagasi H.** Elevated blood lead concentrations

in essential tremor: a case-control study in Mersin, Turkey. *Environmental health perspectives.* 2007; 115(11): 1564–8. DOI: https://doi.org/10.1289/ehp.10352

76. **Ayuso P, Agundez JA, Alonso-Navarro H, Martinez C, Benito-Leon J, Ortega-Cubero S,** et al. Heme Oxygenase 1 and 2 Common Genetic Variants and Risk for Essential Tremor. *Medicine.* 2015; 94(24): e968. DOI: https://doi.org/10.1097/MD.0000000000000968

77. **Ayuso P, Martinez C, Pastor P, Lorenzo-Betancor O, Luengo A, Jimenez-Jimenez FJ,** et al. An association study between Heme oxygenase-1 genetic variants and Parkinson's disease. *Frontiers in cellular neuroscience.* 2014; 8: 298. DOI: https://doi.org/10.3389/fncel.2014.00298

78. **Zhang ZT, He YC, Ma XJ, Li DY, Lu GC.** Association between vitamin D receptor gene polymorphisms and susceptibility to Parkinson's disease: a meta-analysis. *Neuroscience letters.* 2014; 578: 122–7. DOI: https://doi.org/10.1016/j.neulet.2014.06.051

79. **Weisskopf MG, Weuve J, Nie H, Saint-Hilaire MH, Sudarsky L, Simon DK,** et al. Association of cumulative lead exposure with Parkinson's disease. *Environmental health perspectives.* 2010; 118(11): 1609–13. DOI: https://doi.org/10.1289/ehp.1002339

80. **Agundez JAG, Garcia-Martin E, Alonso-Navarro H, Ayuso P, Esguevillas G, Benito-Leon J,** et al. Delta-amino-levulinic acid dehydratase gene and essential tremor. *European journal of clinical investigation.* 2017; 47(5): 348–56. DOI: https://doi.org/10.1111/eci.12742

81. **Sazci A, Uren N, Idrisoglu HA, Ergul E.** The rs2228570 Variant of the Vitamin D Receptor Gene is Associated with Essential Tremor. *Neuroscience bulletin.* 2019; 35(2): 362–4. DOI: https://doi.org/10.1007/s12264-018-0287-6

82. **Greggio E, Jain S, Kingsbury A, Bandopadhyay R, Lewis P, Kaganovich A,** et al. Kinase activity is required for the toxic effects of mutant LRRK2/dardarin. *Neurobiology of disease.* 2006; 23(2): 329–41. DOI: https://doi.org/10.1016/j.nbd.2006.04.001

83. **Heckman MG, Elbaz A, Soto-Ortolaza AI, Serie DJ, Aasly JO, Annesi G,** et al. Protective effect of LRRK2 p.R1398H on risk of Parkinson's disease is independent of MAPT and SNCA variants. *Neurobiology of aging.* 2014; 35(1): 266. e5–14.

84. **Ng ASL, Ng EYL, Tan YJ, Prakash KM, Au WL, Tan LCS,** et al. Case-control analysis of LRRK2 protective variants in Essential Tremor. *Scientific reports.* 2018; 8(1): 5346. DOI: https://doi.org/10.1038/s41598-018-23711-w

85. **Haugarvoll K, Toft M, Ross OA, White LR, Aasly JO, Farrer MJ.** Variants in the LRRK1 gene and susceptibility to Parkinson's disease in Norway. *Neuroscience letters.* 2007; 416(3): 299–301. DOI: https://doi.org/10.1016/j.neulet.2007.02.020

86. **Chao YX, Ng EY, Tan L, Prakash KM, Au WL, Zhao Y,** et al. Lrrk2 R1628P variant is a risk factor for essential tremor. *Scientific reports.* 2015; 5: 9029. DOI: https://doi.org/10.1038/srep09029

87. **Chen H, Yuan L, Song Z, Deng X, Yang Z, Gong L,** et al. Genetic Analysis of LRRK1 and LRRK2 Variants in Essential Tremor Patients. *Genetic testing and molecular biomarkers.* 2018; 22(6): 398–402. DOI: https://doi.org/10.1089/gtmb.2017.0277

88. **Tan EK, Lee J, Lim HQ, Yuen Y, Zhao Y.** Essential tremor and the common LRRK2 G2385R variant. *Parkinsonism & related disorders.* 2008; 14(7): 569–71. DOI: https://doi.org/10.1016/j.parkreldis.2007.12.003

89. **Clark LN, Kisselev S, Park N, Ross B, Verbitsky M, Rios E,** et al. Mutations in the Parkinson's disease genes, Leucine Rich Repeat Kinase 2 (LRRK2) and Glucocerebrosidase (GBA), are not associated with essential tremor. *Parkinsonism & related disorders.* 2010; 16(2): 132–5. DOI: https://doi.org/10.1016/j.parkreldis.2009.05.008

90. **Tan EK, Matsuura T, Nagamitsu S, Khajavi M, Jankovic J, Ashizawa T.** Polymorphism of NACP-Rep1 in Parkinson's disease: an etiologic link with essential tremor? *Neurology.* 2000; 54(5): 1195–8. DOI: https://doi.org/10.1212/WNL.54.5.1195

91. **Pigullo S, Di Maria E, Marchese R, Bellone E, Gulli R, Scaglione C,** et al. Essential tremor is not associated with alpha-synuclein gene haplotypes. *Movement disorders: official journal of the Movement Disorder Society.* 2003; 18(7): 823–6. DOI: https://doi.org/10.1002/mds.10421

92. **Ross OA, Conneely KN, Wang T, Vilarino-Guell C, Soto-Ortolaza AI, Rajput A,** et al. Genetic variants of alpha-synuclein are not associated with essential tremor. *Movement disorders: official journal of the Movement Disorder Society.* 2011; 26(14): 2552–6. DOI: https://doi.org/10.1002/mds.23909

93. **Riboldi GM, Di Fonzo AB.** GBA, Gaucher Disease, and Parkinson's Disease: From Genetic to Clinic to New Therapeutic Approaches. *Cells.* 2019; 8(4). DOI: https://doi.org/10.3390/cells8040364

94. **Choy FY, Zhang W, Shi HP, Zay A, Campbell T, Tang N,** et al. Gaucher disease among Chinese patients: review on genotype/phenotype correlation from 29 patients and identification of novel and rare alleles. *Blood cells, molecules & diseases.* 2007; 38(3): 287–93. DOI: https://doi.org/10.1016/j.bcmd.2006.11.003

95. **Sun QY, Guo JF, Han WW, Zuo X, Wang L, Yao LY,** et al. Genetic association study of glucocerebrosidase gene L444P mutation in essential tremor and multiple system atrophy in mainland China. *Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia.* 2013; 20(2): 217–9. DOI: https://doi.org/10.1016/j.jocn.2012.01.055

96. **Im SY, Kim YE, Kim YJ.** Genetics of Progressive Supranuclear Palsy. *Journal of movement disorders.*

2015; 8(3): 122–9. DOI: https://doi.org/10.14802/jmd.15033

97. **Zabetian CP, Hutter CM, Factor SA, Nutt JG, Higgins DS, Griffith A,** et al. Association analysis of MAPT H1 haplotype and subhaplotypes in Parkinson's disease. *Annals of neurology.* 2007; 62(2): 137–44. DOI: https://doi.org/10.1002/ana.21157

98. **Boeve BF, Hutton M.** Refining frontotemporal dementia with parkinsonism linked to chromosome 17: introducing FTDP-17 (MAPT) and FTDP-17 (PGRN). *Archives of neurology.* 2008; 65(4): 460–4. DOI: https://doi.org/10.1001/archneur.65.4.460

99. **Vilarino-Guell C, Soto-Ortolaza AI, Rajput A, Mash DC, Papapetropoulos S, Pahwa R,** et al. MAPT H1 haplotype is a risk factor for essential tremor and multiple system atrophy. *Neurology.* 2011; 76(7): 670–2. DOI: https://doi.org/10.1212/WNL.0b013e31820c30c1

100. **Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P,** et al. H1-MAPT and the risk for familial essential tremor. *PloS one.* 2012; 7(7): e41581. DOI: https://doi.org/10.1371/journal.pone.0041581

101. **Clark LN, Liu X, Parmalee NL, Hernandez N, Louis ED.** The microtubule associated protein tau H1 haplotype and risk of essential tremor. *European journal of neurology.* 2014; 21(7): 1044–8. DOI: https://doi.org/10.1111/ene.12335

102. **Dardiotis E, Aloizou AM, Siokas V, Patrinos GP, Deretzi G, Mitsias P,** et al. The Role of MicroRNAs in Patients with Amyotrophic Lateral Sclerosis. *Journal of molecular neuroscience: MN.* 2018; 66(4): 617–28. DOI: https://doi.org/10.1007/s12031-018-1204-1

103. **Mackenzie IR, Rademakers R, Neumann M.** TDP-43 and FUS in amyotrophic lateral sclerosis and frontotemporal dementia. *The Lancet Neurology.* 2010; 9(10): 995–1007. DOI: https://doi.org/10.1016/S1474-4422(10)70195-2

104. **Merner ND, Girard SL, Catoire H, Bourassa CV, Belzil VV, Riviere JB,** et al. Exome sequencing identifies FUS mutations as a cause of essential tremor. *American journal of human genetics.* 2012; 91(2): 313–9. DOI: https://doi.org/10.1016/j.ajhg.2012.07.002

105. **Rajput A, Rajput AH, Rajput ML, Encarnacion M, Bernales CQ, Ross JP,** et al. Identification of FUS p.R377W in essential tremor. *European journal of neurology.* 2014; 21(2): 361–3. DOI: https://doi.org/10.1111/ene.12231

106. **Wu YR, Foo JN, Tan LC, Chen CM, Prakash KM, Chen YC,** et al. Identification of a novel risk variant in the FUS gene in essential tremor. *Neurology.* 2013; 81(6): 541–4. DOI: https://doi.org/10.1212/WNL.0b013e31829e700c

107. **Ortega-Cubero S, Lorenzo-Betancor O, Lorenzo E, Alonso E, Coria F, Pastor MA,** et al. Fused in Sarcoma (FUS) gene mutations are not a frequent cause of essential tremor in Europeans. *Neurobiology of aging.* 2013; 34(10): 2441. e9–.e11. DOI: https://doi.org/10.1016/j.neurobiolaging.2013.04.024

108. **Parmalee N, Mirzozoda K, Kisselev S, Merner N, Dion P, Rouleau G,** et al. Genetic analysis of the FUS/TLS gene in essential tremor. *European journal of neurology.* 2013; 20(3): 534–9. DOI: https://doi.org/10.1111/ene.12023

109. **Labbe C, Soto-Ortolaza AI, Rayaprolu S, Harriott AM, Strongosky AJ, Uitti RJ,** et al. Investigating the role of FUS exonic variants in essential tremor. *Parkinsonism & related disorders.* 2013; 19(8): 755–7. DOI: https://doi.org/10.1016/j.parkreldis.2013.03.005

110. **Zheng W, Deng X, Liang H, Song Z, Gao K, Yang Y,** et al. Genetic analysis of the fused in sarcoma gene in Chinese Han patients with essential tremor. *Neurobiology of aging.* 2013; 34(8): 2078. e3–4. DOI: https://doi.org/10.1016/j.neurobiolaging.2013.03.001

111. **Hopfner F, Stevanin G, Muller SH, Mundwiller E, Bungeroth M, Durr A,** et al. The impact of rare variants in FUS in essential tremor. *Movement disorders: official journal of the Movement Disorder Society.* 2015; 30(5): 721–4. DOI: https://doi.org/10.1002/mds.26145

112. **Guengerich FP.** Cytochrome p450 enzymes in the generation of commercial products. *Nature Reviews Drug Discovery.* 2002; 1(5): 359–66. DOI: https://doi.org/10.1038/nrd792

113. **Davis DA.** CME and the pharmaceutical industry: two worlds, three views, four steps. *CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2004; 171(2): 149–50. DOI: https://doi.org/10.1503/cmaj.1040361

114. **Alonso-Navarro H, Martinez C, Garcia-Martin E, Benito-Leon J, Garcia-Ferrer I, Vazquez-Torres P,** et al. CYP2C19 polymorphism and risk for essential tremor. *European neurology.* 2006; 56(2): 119–23. DOI: https://doi.org/10.1159/000095702

115. **Pal PK.** Guidelines for management of essential tremor. *Annals of Indian Academy of Neurology.* 2011; 14(Suppl 1): S25–8. DOI: https://doi.org/10.4103/0972-2327.83097

116. **Martinez C, Garcia-Martin E, Alonso-Navarro H, Jimenez-Jimenez FJ, Benito-Leon J, Garcia-Ferrer I,** et al. Changes at the CYP2C locus and disruption of CYP2C8/9 linkage disequilibrium in patients with essential tremor. *Neuromolecular medicine.* 2007; 9(2): 195–204. DOI: https://doi.org/10.1007/BF02685892

117. **Bertilsson L, Dahl ML, Dalen P, Al-Shurbaji A.** Molecular genetics of CYP2D6: clinical relevance with focus on psychotropic drugs. *British journal of clinical pharmacology.* 2002; 53(2): 111–22. DOI: https://doi.org/10.1046/j.0306-5251.2001.01548.x

118. **Agundez JA, Jimenez-Jimenez FJ, Tejeda R, Ledesma MC, Orti-Pareja M, Gasalla T,** et al. CYP2D6 polymorphism is not associated with essential tremor.

*European neurology.* 1997; 38(2): 99–104. DOI: https://doi.org/10.1159/000113168

119. **Dardiotis E, Siokas V, Pantazi E, Dardioti M, Rikos D, Xiromerisiou G,** et al. A novel mutation in TREM2 gene causing Nasu-Hakola disease and review of the literature. *Neurobiology of aging.* 2017; 53: 194. e13–.e22. DOI: https://doi.org/10.1016/j.neurobiolaging.2017.01.015

120. **Yeh FL, Hansen DV, Sheng M.** TREM2, Microglia, and Neurodegenerative Diseases. *Trends in molecular medicine.* 2017; 23(6): 512–33. DOI: https://doi.org/10.1016/j.molmed.2017.03.008

121. **Rikos D, Siokas V, Aloizou AM, Tsouris Z, Aslanidou P, Koutsis G,** et al. TREM2 R47H (rs75932628) variant is unlikely to contribute to Multiple Sclerosis susceptibility and severity in a large Greek MS cohort. *Multiple sclerosis and related disorders.* 2019; 35: 116–8. DOI: https://doi.org/10.1016/j.msard.2019.07.007

122. **Ortega-Cubero S, Lorenzo-Betancor O, Lorenzo E, Agundez JA, Jimenez-Jimenez FJ, Ross OA,** et al. TREM2 R47H variant and risk of essential tremor: a cross-sectional international multicenter study. *Parkinsonism & related disorders.* 2015; 21(3): 306–9. DOI: https://doi.org/10.1016/j.parkreldis.2014.12.010

123. **Emamalizadeh B, Jamshidi J, Movafagh A, Ohadi M, Khaniani MS, Kazeminasab S,** et al. RIT2 Polymorphisms: Is There a Differential Association? *Molecular neurobiology.* 2017; 54(3): 2234–40. DOI: https://doi.org/10.1007/s12035-016-9815-4

124. **Ledesma MC, Garcia-Martin E, Alonso-Navarro H, Martinez C, Jimenez-Jimenez FJ, Benito-Leon J,** et al. The nonsynonymous Thr105Ile polymorphism of the histamine N-methyltransferase is associated to the risk of developing essential tremor. *Neuromolecular medicine.* 2008; 10(4): 356–61. DOI: https://doi.org/10.1007/s12017-008-8040-3

125. **Keeling BH, Vilarino-Guell C, Soto-Ortolaza AI, Ross OA, Uitti RJ, Rajput A,** et al. Histamine N-methyltransferase Thr105Ile is not associated with Parkinson's disease or essential tremor. *Parkinsonism & related disorders.* 2010; 16(2): 112–4. DOI: https://doi.org/10.1016/j.parkreldis.2009.08.011

126. **Siokas V, Aloizou AM, Tsouris Z, Michalopoulou A, Mentis AA, Dardiotis E.** Risk Factor Genes in Patients with Dystonia: A Comprehensive Review. *Tremor and other hyperkinetic movements (New York, NY).* 2018; 8: 559.

127. **Sazci A, Ergul E, Bayulkem K.** Association of the C677T and A1298C polymorphisms of methylenetetrahydrofolate reductase gene in patients with essential tremor in Turkey. *Movement disorders: official journal of the Movement Disorder Society.* 2004; 19(12): 1472–6. DOI: https://doi.org/10.1002/mds.20254

128. **Chen CM, Hou YT, Liu JY, Wu YR, Lin CH, Fung HC,** et al. PPP2R2B CAG repeat length in the Han Chinese in Taiwan: Association analyses in neurological and psychiatric disorders and potential functional implications. *American journal of medical genetics Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics.* 2009; 150b(1): 124–9. DOI: https://doi.org/10.1002/ajmg.b.30785

129. **Martinez C, Garcia-Martin E, Alonso-Navarro H, Benito-Leon J, Puertas I, Rubio L,** et al. Glutathione-S-transferase P1 polymorphism and risk for essential tremor. *European journal of neurology.* 2008; 15(3): 234–8. DOI: https://doi.org/10.1111/j.1468-1331.2007.02040.x

130. **Dardiotis E, Aloizou AM, Siokas V, Tsouris Z, Rikos D, Marogianni C,** et al. Paraoxonase-1 genetic polymorphisms in organophosphate metabolism. *Toxicology.* 2019; 411: 24–31. DOI: https://doi.org/10.1016/j.tox.2018.10.012

131. **Costa LG, Giordano G, Cole TB, Marsillach J, Furlong CE.** Paraoxonase 1 (PON1) as a genetic determinant of susceptibility to organophosphate toxicity. *Toxicology.* 2013; 307: 115–22. DOI: https://doi.org/10.1016/j.tox.2012.07.011

132. **Deng H, Xie WJ, Le WD, Huang MS, Jankovic J.** Genetic analysis of the GABRA1 gene in patients with essential tremor. *Neuroscience letters.* 2006; 401(1–2): 16–9. DOI: https://doi.org/10.1016/j.neulet.2006.02.066

133. **Thier S, Kuhlenbaumer G, Lorenz D, Nothnagel M, Nebel A, Christensen K,** et al. GABA(A) receptor- and GABA transporter polymorphisms and risk for essential tremor. *European journal of neurology.* 2011; 18(8): 1098–100. DOI: https://doi.org/10.1111/j.1468-1331.2010.03308.x

134. **Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P,** et al. Gamma-aminobutyric acid GABRA4, GABRE, and GABRQ receptor polymorphisms and risk for essential tremor. *Pharmacogenetics and genomics.* 2011; 21(7): 436–9. DOI: https://doi.org/10.1097/FPC.0b013e328345bec0

135. **Garcia-Martin E, Martinez C, Alonso-Navarro H, Benito-Leon J, Lorenzo-Betancor O, Pastor P,** et al. Gamma-aminobutyric acid (GABA) receptor rho (GABRR) polymorphisms and risk for essential tremor. *Journal of neurology.* 2011; 258(2): 203–11. DOI: https://doi.org/10.1007/s00415-010-5708-z

136. **Deng H, Le WD, Guo Y, Huang MS, Xie WJ, Jankovic J.** Extended study of A265G variant of HS1BP3 in essential tremor and Parkinson disease. *Neurology.* 2005; 65(4): 651–2. DOI: https://doi.org/10.1212/01.wnl.0000173033.32535.23

137. **Higgins JJ, Lombardi RQ, Pucilowska J, Jankovic J, Tan EK, Rooney JP.** A variant in the HS1-BP3 gene is associated with familial essential tremor. *Neurology.* 2005; 64(3): 417–21. DOI: https://doi.org/10.1212/01.WNL.0000153481.30222.38

138. **Martinez C, Garcia-Martin E, Alonso-Navarro H, Benito-Leon J, Puertas I, Rubio L,** et al. Alcohol dehydrogenase 2 genotype and allelic variants are not associated with the risk for essential tremor. *Clinical neuropharmacology.* 2007; 30(4): 196–200.

139. **Pigullo S, Di Maria E, Marchese R, Assini A, Bellone E, Scaglione C,** et al. No evidence of association between CAG expansions and essential tremor in a large cohort of Italian patients. *Journal of neural transmission (Vienna, Austria: 1996).* 2001; 108(3): 297–304. DOI: https://doi.org/10.1007/s007020170075

140. **Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Agundez JA.** SLC1A2 rs3794087 variant and risk for essential tremor: a systematic review and meta-analysis. *Pharmacogenetics and genomics.* 2015; 25(11): 564–8. DOI: https://doi.org/10.1097/FPC.0000000000000171

141. **Jimenez-Jimenez FJ, Garcia-Martin E, Lorenzo-Betancor O, Pastor P, Alonso-Navarro H, Agundez JA.** LINGO1 and risk for essential tremor: results of a meta-analysis of rs9652490 and rs11856808. *Journal of the neurological sciences.* 2012; 317(1–2): 52–7. DOI: https://doi.org/10.1016/j.jns.2012.02.030

142. **Kuhlenbaumer G, Hopfner F, Deuschl G.** Genetics of essential tremor: meta-analysis and review. *Neurology.* 2014; 82(11): 1000–7. DOI: https://doi.org/10.1212/WNL.0000000000000211

143. **Mao X, Wang T, Liu M, Chang X, Li N, Gu Y,** et al. Meta-analysis of the influence of DRD3 Ser9Gly variant on susceptibility for essential tremor. *Journal of clinical neuroscience: official journal of the Neurosurgical Society of Australasia.* 2013; 20(12): 1644–9. DOI: https://doi.org/10.1016/j.jocn.2013.03.023

144. **Deuschl G, Bain P, Brin M.** Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Movement disorders: official journal of the Movement Disorder Society.* 1998; 13(Suppl 3): 2–23. DOI: https://doi.org/10.1002/mds.870131303

145. **Louis ED, Ford B, Lee H, Andrews H, Cameron G.** Diagnostic criteria for essential tremor: a population perspective. *Archives of neurology.* 1998; 55(6): 823–8. DOI: https://doi.org/10.1001/archneur.55.6.823

146. **Louis ED, Jiang W, Pellegrino KM, Rios E, Factor-Litvak P, Henchcliffe C,** et al. Elevated blood harmane (1-methyl-9H-pyrido[3,4-*b*]indole) concentrations in essential tremor. *Neurotoxicology.* 2008; 29(2): 294–300. DOI: https://doi.org/10.1016/j.neuro.2007.12.001

147. **Jankovic J.** Essential tremor: clinical characteristics. *Neurology.* 2000; 54(11 Suppl 4): S21–5.

148. **Louis ED, Ottman R, Ford B, Pullman S, Martinez M, Fahn S,** et al. The Washington Heights-Inwood Genetic Study of Essential Tremor: methodologic issues in essential-tremor research. *Neuroepidemiology.* 1997; 16(3): 124–33. DOI: https://doi.org/10.1159/000109681

149. **Bain P, Brin M, Deuschl G, Elble R, Jankovic J, Findley L,** et al. Criteria for the diagnosis of essential tremor. *Neurology.* 2000; 54(11 Suppl 4): S7.

150. **Louis ED, Ford B, Frucht S, Barnes LF, X-Tang M, Ottman R.** Risk of tremor and impairment from tremor in relatives of patients with essential tremor: a community-based family study. *Annals of neurology.* 2001; 49(6): 761–9. DOI: https://doi.org/10.1002/ana.1022