Tremor and Other Hyperkinetic Movements

The Genetic Architecture of Essential Tremor

REVIEWS

HILARY SHEPHERD-MACADIE
NICOLA PAVESE
DAVID LEDINGHAM
ANTONELLA MACEROLLO
JIBRIL OSMAN FARAH

*Author affiliations can be found in the back matter of this article

ubiquity press

ABSTRACT

Background: Essential tremor (ET) is the most common adult movement disorder with a reported global prevalence of 0.32%–0.9%, rising to 4.6–6.3% in those >65 years [1–5]. Autosomal dominant patterns of inheritance have been reported in some multiplex ET families; genetic studies continue to yield heterogenous results [6, 7]. Despite numerous reported genes and loci, replication has been inconsistent and the relative strength of genetic findings varies considerably [8, 9].

Objective: To provide a comprehensive overview of advances in ET genetics over the last decade, synthesising evidence across contemporary genetic approaches and identifying key gaps and priorities for future research.

Methods: PubMed, Scopus and Web of Science were searched for human genetic studies of ET published between 2015 and 2025. Eligible studies included candidate-gene, genome-wide association, family-based sequencing and other genomic approaches. Following screening and hand-searching of reference lists, 33 studies were included.

Results: Genetic findings were highly heterogeneous. Evidence included common susceptibility loci with small effects, rare family-specific variants, repeat expansions and candidate-gene associations, but independent replication was limited. Most studies also used diagnostic criteria predating the 2018 International Parkinson and Movement Disorder Society (IPMDS) tremor classification.

Discussion: Current evidence supports a complex and heterogeneous genetic architecture for ET rather than a single genetic model. Larger ancestry-diverse cohorts, consistent longitudinal phenotyping, independent replication and integration of genomic findings with functional and molecular approaches are required to establish biologically and clinically relevant genetic determinants.

CORRESPONDING AUTHORS:
Dr. Hilary Shepherd-Macadie
The Walton Centre NHS Trust, Lower Lane, Liverpool L9 7LJ, United Kingdom
Hilary. Shepherd-Macadie@liverpool.ac.uk

Prof. Antonella Macerollo
The Walton Centre NHS Trust, Lower Lane, Liverpool L9 7LJ, United Kingdom; Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, United Kingdom
a.macerollo@liverpool.ac.uk

KEYWORDS:
genetics; genomic; GWAS; variant; essential tremor

TO CITE THIS ARTICLE:
Shepherd-Macadie H, Ledingham D, Osman Farah J, Pavese N, Macerollo A. The Genetic Architecture of Essential Tremor. *Tremor and Other Hyperkinetic Movements*. 2026; 16(1): 64, pp. 1–14. DOI: https://doi.org/10.5334/tohm.1240

1. INTRODUCTION

Essential tremor (ET) is the most common adult movement disorder with a reported global prevalence of 0.32%–0.9%, rising to 4.6–6.3% in those 65 years or older [1–3, 10]. ET is characterized by a visible and persistent action and/or postural tremor at frequencies 4–12 Hz, that predominantly affect the upper limbs (95%) but can include the head (41%) and voice (29%) [11, 12]. Additional neurological symptoms have been reported in addition to the classic tremor including dystonic posturing, rest tremor and gait impairment, as well as non-motor symptoms of memory impairment, depression and anxiety disorder [13–15]. The term "ET-plus" has been coined to describe these ET cases and highlights a new complexity in how the disease is viewed (see Table 1) [16]. Misdiagnosis is also common with a reported rate of 37–50% [17].

The pathophysiological mechanism behind ET is still unknown [18–20]. The traditional "olivary model", which attributed ET to issues with the central electrophysiological circuit, has subsequently evolved to a distributed circuit that encompasses the olivocerebelothalamic loop with the cerebellum as its central node [20]. Post-mortem studies have failed to identify a common olivary pathology. Though there have been reports of some findings of interest such as Lewy bodies within the brainstem, Purkinje cell loss and axonal swellings, known as torpedoes [10, 21, 22]. These findings remain debated and have not been consistently replicated [8, 10]. This variability may reflect an inherent biological heterogeneity within ET itself or may arise due to methodological differences and/or clinical misclassification [8, 10].

Increasing recognition of ET as a heterogeneous condition has driven growing interest in its genetic basis [6, 23–25]. Researchers have sought to exploit the well-established hereditary nature of ET to identify specific genes or genetic pathways that could serve as potential biomarker or therapeutic targets [6, 24–26]. Autosomal dominant patterns of inheritance have been reported in some multiplex ET families, however, the population-level inheritance of ET is complex and is not explained by a single Mendelian model [6, 7]. Sporadic disease is common, penetrance is variable, and bilineal inheritance may occur [27, 28]. Furthermore, ascertainment of affected relatives may be influenced by factors like age, tremor severity and the methods used to identify and examine affected family members [27, 28]. Despite over 20 or more genes being associated with the increased risk of developing ET, the reproducibility in follow up studies continues to be poor [26]. Penetrance in familial ET appears to be age dependent and remains incompletely defined. In an early study of hereditary ET, penetrance was reported to be virtually complete by 65 years of age. However, subsequent studies have questioned whether penetrance is complete even in older individuals [27]. A bimodal distribution of age at onset has been proposed, comprising an early-onset group (<24 years) and a late-onset group (>46 years) [29]. The early-onset phenotype involves the classical symptoms associated with ET of an alcohol-responsive tremor and a strong family inheritance where the later onset have more "ET-plus" symptoms associated [2, 29, 30]. Collectively, these findings provide further evidence for the genetic heterogeneity of ET and could even suggest the existence

FEATURE	PURE ET	ET-PLUS
Core tremor type	Bilateral action/postural tremor	Same core action tremor
Distribution	Hands ± head, voice, jaw	Same as ET
Rest tremor	Absent	May be minimal/questionable
Gait	Normal	Mild gait imbalance/impaired tandem gait
Cerebellar signs	None	Subtle intention tremor or mild ataxia
Dystonia	None	Mild dystonic posturing may be present
Bradykinesia	Absent	At most equivocal/very mild (not meeting PD criteria)
Cognitive function	Normal	Mild cognitive complaints possible
Other neurological signs	None	Soft neurological signs of uncertain significance
Progression	Usually slow, isolated tremor	Similar tremor but with additional features
Meets criteria for another disorder	No	Still NO–otherwise it is not ET-plus

Table 1 Summary of characteristics of pure ET and ET-PLUS.

of at least two phenotypic subgroups that may arise from independent genetic mechanisms [9, 24].

The aim of the current narrative review is to provide a comprehensive overview of advances in the genetics of ET over the last decade, synthesising evidence across contemporary genetic approaches and identifying key gaps and priorities for future research.

2. METHODS

Due to the anticipated heterogeneity in study designs, genetic approaches, and phenotypic definitions, a formal systematic review was not planned. Instead, a structured literature search was undertaken to identify relevant genetic studies of ET published between 1 January 2015 and 31 December 2025.

PubMed, Scopus, and Web of Science (WoS) databases were searched using the search terms outlined in Supplementary Information Section 1. The initial searches identified 767 records from PubMed, 90 from Scopus, and 1,079 from WoS. Searches were restricted to full-text articles published in English involving human adult participants. Titles and abstracts were initially screened by the primary author to remove duplicate and clearly irrelevant records, leaving 182 records from PubMed and 18 from Scopus for further assessment. No additional eligible records were identified from WoS following removal of duplicates and screening.

Potentially relevant articles were assessed against predefined eligibility criteria. Original human genetic studies were considered for inclusion, including genetic association studies, case–control or cohort studies, genome-wide association studies (GWAS), family-based sequencing studies, and other relevant genomic approaches. Reviews, meta-analyses, case reports, descriptive case series, and conference abstracts or proceedings without a subsequent full peer-reviewed publication were excluded. Full inclusion and exclusion criteria are provided in Supplementary Data Tables 1 and 2, respectively. Following assessment, 21 articles identified through the database searches met the eligibility criteria and were included. A further 12 eligible articles were identified through further hand-searches of the reference lists resulting in a final total of 33 studies included in the narrative review.

Data from the included studies were extracted and summarised by the primary author. For each study, the authors, year and country of publication, ancestry of the study population, sample size, ET diagnostic criteria applied, study design, gene or locus investigated, genetic variant or signal and variant class, allele frequency, segregation pattern, replication status, functional evidence, implicated biological pathway(s), key findings, and overall strength of evidence were recorded where available. These data are presented in Supplementary Tables 4, 5 and 6.

Following peer review, two additional studies were incorporated to address specific points raised by the reviewers. These studies were used to provide additional context for the GWAS and replication evidence and were not included in the original study-selection dataset or quantitative summaries.

3. RESULTS

3.1 EVOLUTION AND TYPES OF GENETIC EVIDENCE IN ESSENTIAL TREMOR

Genetic studies of ET have evolved considerably over the last two decades, progressing from family-based linkage and candidate-gene studies to genome-wide association studies (GWAS), whole-exome sequencing (WES), whole-genome sequencing (WGS), and repeat-expansion analyses (summarised in Table 2) [9, 26]. These approaches investigate different components of genetic architecture and consequently provide different forms and strengths of evidence for an association with ET.

Early family-based linkage studies investigated chromosomal regions co-segregating with tremor in families, including the reported ETM1, ETM2 and ETM3 loci [9, 31]. Family-based WES and WGS facilitated investigation of rare protein-coding and genome-wide variants respectively, within affected families helping to nominate possible rare family-specific variants [9, 31]. In contrast, GWAS approach enabled whole genome investigation to identify potential candidate loci from common SNP variants, then comparing allele frequencies between ET cases and unaffected controls [32]. More recently, larger GWAS and meta-analyses have increased detection of common susceptibility loci with small individual effect sizes due to their increased power [33]. Repeat expansion analyses have allowed for broader exploration of repeat variation underlying the potential genetic architecture of ET [34].

Across the included studies, established diagnostic criteria for ET were clearly reported in 28/31 studies (90.3%). However, 29/31 studies (93.5%) used diagnostic frameworks that pre-dated the 2018 International Parkinson and Movement Disorder Society (IPMDS) tremor classification [15]. Only one study (3.2%) explicitly applied the 2018 IPMDS criteria and formally considered ET-plus. Formal longitudinal or repeat diagnostic reassessment was uncommon, being reported in only 3/31 studies (9.7%) (Supplementary Table 3).

Given the heterogeneity of diagnostic criteria, study designs, phenotypes and levels of replication across the ET literature, genetic findings should not be accorded equal

METHOD	VARIANTS	VARIANT FREQUENCY	SAMPLE SIZE	OUTPUT	HYPOTHESIS/ EXPLANATION	BENEFITS	LIMITATIONS
Family based Linkage Studies (FBLS)	Genetic markers co-inherited within families	Rare variants (<1%)	Family; small-moderate	Broad chromosomal region linked to disease	Disease-causing mutations are inherited within families together with nearby genetic markers.	- Detects rare, highly penetrant variants - Robust to population stratification - Useful for Mendelian disorders	- Low resolution (large, linked regions) - Limited utility for complex/ polygenic diseases - Requires large pedigrees
Candidate-gene case–control studies (CGCC)	Single nucleotide polymorphisms (SNPs) in Specific preselected genes.	Common variants (>5%)	Hundreds to thousands	Association in preselected genes	Tests predefined genes selected based on prior biological knowledge for association with a disease by comparing allele frequencies between cases and controls.	- Simple and relatively inexpensive - Focused hypothesis-driven approach - Easier statistical interpretation	- Strong bias from incorrect gene selection - Poor reproducibility - Limited ability to detect novel variants - Often underpowered
Whole-exome sequencing (WES)	Coding-region variants (exons only; ~1–2% of genome)	Mainly rare (<1%) and low-frequency variants (1–5%)	Hundreds to thousands	Rare coding mutations/causal variants	Many disease-causing mutations lie in protein-coding regions because coding changes directly alter protein function.	- Cost-effective compared with WGS - Enriches for variants with high functional impact - Well suited for rare disease discovery	- Misses non-coding and regulatory variants - Uneven coverage across exons - Structural variants poorly detected
Whole-genome sequencing (WGS)	All genomic variants including coding and non-coding regions	Rare (<1%), low-frequency (1–5%), and common variants (>5%)	Thousands+ depending on disease	Comprehensive genome-wide variant discovery	Disease-associated variants may occur anywhere in the genome, including regulatory/non-coding regions.	- Comprehensive variant detection - Identifies structural, regulatory, and non-coding variants - Uniform coverage	- High cost and data storage demands - Complex analysis and interpretation - Many variants of uncertain significance
Early Genome-wide association studies (GWAS)	Hundreds of thousands to millions of common Single nucleotide polymorphisms (SNPs)	Common variants(>5%)	Thousands to tens of thousands	Associated loci/SNPs	Common disease–common variant states common diseases are influenced by common variants with modest effects.	- Unbiased, approach - Highly reproducible with large samples - Effective for complex traits	- Identifies loci, not causal variants - Mostly detects common variants with small effects - Requires very large sample sizes
Late Genome-wide association studies (GWAS)	Denser SNP arrays to capture more genetic variation+ imputation to predict further variant combinations possible via inheritance+ some sequencing using either WES/WGS to add rare variant coverage	Common (>5%) & low-frequency variants (1–5%)	Hundreds of thousands to millions	Polygenic risk loci, PRS, fine mapping	Polygenic model describes complex diseases arise from thousands of variants each contributing tiny effects.	- Huge statistical power; - enables Polygenic Risk Score, the estimate of a person's genetic predisposition to a disease or trait.	- Association ≠ causation, the associated SNP is often not the true causal variant. - Ancestry bias/poor PRS transferability - Missing heritability & tiny effect sizes - Most variants have extremely small effects
Repeat expansion analysis	Short tandem repeat expansions (e.g. trinucleotide repeats)	Rare variants	Small targeted cohorts or families	Expanded repeats disrupt gene/protein function and may show anticipation	Expansion of unstable repetitive DNA beyond a threshold disrupts gene function and causes disease.	- detects variants missed by GWAS/ WES as very long repeats exceed short-read sequencing capability.	- Technically challenging for very long repeats

Table 2 Comparison of Genetic Study Designs.

EVIDENCE DOMAIN	PRINCIPAL GENES/ LOCI FINDINGS	SUPPORTING STUDIES	REPLICATION/EVIDENCE PATTERN	OVERALL INTERPRETATION
Replicated common susceptibility loci	STK32B; PPARGC1A; CTNNA3	10; *Liao et al. (2022); supported by 33	GWAS evidence; PPARGC1A-region signal supported in later large GWAS/meta-analysis; SNP-based heritability evidence	Strongest evidence for a common-variant contribution to ET susceptibility
Rare family-specific variants	CACNA1G, SLIT3, TENM4, SCN4A, SORT1	1, 9, 12, 13, 14, 22, 25, 26, 28, 29, 31	Mostly family-specific; variable segregation/function	Suggests genetic heterogeneity, although causality remains unresolved for most variants
Molecular diagnoses/ phenocopies	NOTCH2NLC, FMR1, ataxia-repeat loci	3, 6, 8, 23	NOTCH2NLC reproduced; others largely negative	Some individuals diagnosed clinically with ET may have alternative molecular disorders
Candidate associations	VDR, TREM2, HMOX, LRRK2, MC1R, RIT2; FUS rs1052352	2, 4, 5, 11, 15–21, 24, 27, 30, 32; *Yan et al. (2020)	Mostly isolated, nominal or unreplicated; FUS rs1052352 associated in one Chinese cohort	Exploratory evidence requiring independent replication
Conflicting/inconsistent findings	VDR, TREM2, HMOX1/2, TENM4, FUS, HTRA2; historical LINGO1/SLC1A2	20 & 16, 2, 5 & 21, 22; *Yan et al. (2020)	Discordant or negative replication across populations	Highlights uncertainty in candidate associations and the influence of phenotypic and methodological heterogeneity.

Table 3 Summary of the main genetic evidence and replication patterns in essential tremor studies published between 2015 and 2025.

Note: Studies marked with an * represent additional evidence incorporated following reviewer recommendations. Full results in Supplementary Tables 4 to 7.

weight when evaluating evidence for ET susceptibility or causation [9, 26]. Findings from the included studies were therefore synthesised according to the type and strength of evidence supporting their relationship with ET, including: (1) replicated common susceptibility loci; (2) rare variants proposed in individual families; (3) molecular diagnoses or phenocopies presenting with ET-like tremor; (4) candidate-gene associations with weak or absent replication; and (5) genetic findings with conflicting or inconsistent replication (Summarised in Table 3).

3.1.1 Replicated common susceptibility loci

Müller et al. conducted a two-stage GWAS comprising 2,807 individuals with ET and 6,441 controls of European ancestry [35]. Following the initial discovery stage, the 59 most strongly associated markers were tested in a separate replication cohort within the same study [35]. The study also attempted to replicate previously reported ET susceptibility variants, including *LINGO1* (rs9652490) and *SLC1A2* (rs3794087); however, neither association was confirmed [35].

Among the novel signals identified in the discovery stage, STK32B (rs10937625) and PPARGC1A (rs17590046) showed significant association following Bonferroni correction in the internal replication stage [35]. In contrast, three intronic variants within CTNNA3 were principally supported by the combined discovery and replication analysis: rs12764057 (OR 1.17, 95% CI 1.09–1.26; $P = 1.19 \times 10^{-8}$), rs10822974 (OR 1.16, 95% CI 1.08–1.24; $P = 1.65 \times 10^{-7}$), and rs7903491 (OR 1.10, 95% CI 1.03–1.18; $P = 2.49 \times 10^{-7}$) [35]. Of these, rs12764057 reached the conventional genome-wide significance threshold of $P < 5 \times 10^{-8}$ in the combined analysis, whereas the remaining CTNNA3 signals did not [35]. The minor allele frequencies of the reported variants are summarised in Supplementary Table 5.

A subsequent larger GWAS and meta-analysis by Liao et al. included 7,177 individuals with ET and 475,877 controls of European ancestry across clinical cohorts and population biobanks [33]. Five loci reached genome-wide significance: rs1127215 (OR 1.09, 95% CI 1.06–1.13; $P = 2.76 \times 10^{-8}$), rs17590046 (OR 0.89, 95% CI 0.85–0.93; $P = 1.18 \times 10^{-8}$), rs28562175 (OR 0.92, 95% CI 0.88–0.95; $P = 3.48 \times 10^{-8}$), rs1945016 (OR 1.10, 95% CI 1.06–1.13; $P = 1.26 \times 10^{-8}$), and rs9980363 (OR 1.16, 95% CI 1.12–1.20; $P = 4.92 \times 10^{-14}$) [33]. Notably, rs17590046, previously identified at the *PPARGC1A* locus by Müller et al. received support in a subsequent independent study and substantially larger dataset [36]. Liao et al, reported that this chromosome 4 signal had shown nominal significance in the previous GWAS and was consistent across the cohorts included in their meta-analysis [33, 35].

Functional annotation provided additional biological support for STK32B, with increased STK32B expression reported in the cerebellar cortex of individuals with ET. Expression quantitative trait locus (eQTL) analysis associated the protective minor allele of rs10937625 with reduced cerebellar STK32B expression [35]. Comparable expression

differences were not demonstrated for PPARGC1A or CTNNA3 [35]. Liao et al. extended the functional investigation using transcriptome-wide association, fine-mapping, eQTL and gene-set analyses [33]. Transcriptome-wide association analysis (TWAS) identified *BACE2* and *LINC00323* as significant, with *BACE2*, *LINC00323* and *ANGEL2* reached significance in a brain omnibus analysis. Fine-mapping further prioritised *BACE2*, while functional analyses demonstrated enrichment in the cerebellum, cerebellar hemisphere and axon genesis pathways [33].

Liao et al. also estimated SNV-based heritability at 18.29%, supporting a contribution of common genetic variation to ET susceptibility [33]. However, individual susceptibility variants showed modest effect sizes, consistent with a complex genetic architecture rather than a single common variant of large effect. The strength of replication differs between loci: rs17590046 has cross-study support, whereas the earlier STK32B and CTNNA3 signals have not been consistently reproduced in subsequent independent studies. Furthermore, the five genome-wide significant loci identified by Liao et al. were derived from meta-analysis across constituent cohorts rather than validation in a subsequent external replication cohort. The study was also restricted to European ancestry, with less detailed phenotyping in the population-based cohorts [33]. Further ancestry-diverse studies with independent cross-study replication and functional validation are required to establish the reproducibility and biological relevance of these susceptibility loci.

3.1.2 Rare variants proposed in individual families

Across the WES/WGS studies, approximately 25 candidate genes were implicated through variants either explicitly reported at a Minor Allele Frequency (MAF) or selected using study-defined rare-variant allele-frequency thresholds (Supplementary Table 5). Familial sequencing studies frequently identified different candidate variants across individual pedigrees, with limited recurrence across unrelated families [13, 24, 26].

One familial WES study identified seven possible genes linked to ET from only 14 families, with each proposed gene variant appearing in only one or two families [37]. Extending analysis beyond coding regions to include single nucleotide variants (SNVs), structural variants (SVs) and copy number variants (CNVs), Odgerel et al. performed WGS in 40 individuals from eight ET families and identified candidate genes in 5/8 families (62.5%) [13]. CACNA1G was implicated in one family through the rare missense variant c.1367G>A (p. Arg456Gln; rs116920450), while a SLIT3 c.3505G>C (p. Val1169Leu) variant was identified in another family; both candidates underwent subsequent functional investigation [13].

To increase sensitivity for rare-variant discovery while limiting false-positive findings, Díez-Fairén et al. performed a multistep study incorporating familial segregation, population-level association and gene-based burden analyses [26]. No single gene accounted for ET across the investigated families, with multiple candidate variants instead identified across individual pedigrees. Fifteen rare variants showed co-segregation with ET within individual families [26]. Three variants subsequently showed nominal association with ET: CCDC183 rs749875462 ($p = 0.0087$; OR 4.04, 95% CI 1.26–16.91; allele frequency 1.3% in cases vs 0.3% in controls), MMP10 rs535864157 ($p = 0.0220$; allele frequency 0.5% in cases vs 0% in controls), and GPR151 rs114285050 ($p = 0.0425$; OR 2.69, 95% CI 0.97–8.58; allele frequency 1.3% in cases vs 0.5% in controls)(26). However, none remained significant after Bonferroni correction ($p < 0.0036$) [26]. The subsequent analyses were also conducted within the same underlying population rather than confirming in an independent sample. These findings provide further evidence of genetic heterogeneity but do not establish that this heterogeneity is predominantly attributable to multiple rare variants.

The remaining rare candidate variants genes implicated include RBFOX1, PCDH9, N6AMT1, FUS, TENM4 and SCARB2, among others [24, 37, 38]. However, the strength of evidence supporting individual candidates varies considerably and may include low population allele frequency, co-segregation within individual pedigrees, linkage evidence, recurrence across unrelated families and functional or biological plausibility. These genes should not be regarded as having equivalent levels of evidence for involvement in ET.

3.1.3 Molecular diagnoses and phenocopies presenting with ET-like tremor

A distinct group of findings comprises molecular diagnoses or genetic disorders that may present with an ET-like tremor phenotype rather than representing susceptibility variants for ET itself. Sun et al. identified pathogenic GGC repeat expansions in NOTCH2NLC in approximately 5–6% of selected East Asian ET cohorts/families with co-segregation of the expansion with disease, evidence of genetic anticipation, and pathological inclusions resembling those observed in neuronal intranuclear inclusion disease (NIID) [34]. This frequency should be considered in the context of the East Asian ancestry rather than as an estimate applicable to ET populations in general [34, 39]. NOTCH2NLC expansions are associated with NIID, a heterogeneous neurodegenerative disorder characterised by a broad spectrum of neurological phenotypes, including tremor and parkinsonism [34, 39]. Consequently, expansion-positive individuals presenting clinically with ET

may represent a tremor-predominant NOTCH2NLC-related repeat-expansion disorder or ET phenocopy, rather than establishing NOTCH2NLC as a general susceptibility gene for ET [34, 39].

A similar issue of phenotypic overlap should be considered for CAMTA1, in which pathogenic variants are associated with neurological disorders characterised predominantly by ataxia and other cerebellar features [37]. Reports of CAMTA1 variants in individuals diagnosed with ET should be interpreted cautiously, as these findings may reflect phenotypic overlap or misclassification rather than establishing CAMTA1 as a general susceptibility gene for ET [37].

3.1.4 Candidate-gene associations with weak or absent replication

Candidate-gene case–control (CGCC) studies accounted for over half of the studies reported in this review, with multiple population-specific associations identified (Supplementary Tables 4–6). These CGCC-associated genes, including MAPT, often demonstrate small signals and context-dependent risk effects [9, 23, 26]. Several of these genes can be linked to biologically relevant pathways believed to contribute to broader neurodegenerative dysfunction particularly in the cerebellar region.

The pathways are implicated in neuroinflammation, oxidative stress, vitamin D signalling, and the nigrostriatal degeneration associated with Parkinson's disease (PD) [24, 40–44]. However, most lack independent replication and are best treated as potential modest or population-specific risk modifiers rather than primary causal variants (Supplementary Tables 4–6) [9, 26].

Several studies examined associations between ET and variants in genes previously implicated in PD or related neurodegenerative pathways, including LRRK2, MAPT, SCARB2, N6AMT1, MC1R and TREM2 [24, 44–47]. However, these signals were generally modest, population-specific, and inconsistently replicated [9, 23, 26]. Although they may indicate potentially overlapping molecular pathways worthy of further investigation, candidate-gene associations alone do not establish a shared genetic architecture between ET and PD [9, 23].

3.1.5 Genetic findings with conflicting or inconsistent replication

Several genetic findings initially reported in association with ET have subsequently shown conflicting or inconsistent replication. Earlier studies reported associations between ET and common variants in LINGO1 (rs9652490) and SLC1A2 (rs3794087) [48]. However, Müller et al. subsequently failed to replicate either association in their large GWAS cohort.

Rare variants in FUS were initially reported in families with ET, including p. Pro431Leu, but subsequent studies have not consistently reproduced rare FUS variants across independent families or populations [49]. Yan et al. subsequently sequenced the coding regions of FUS in 238 Chinese patients with ET and 272 controls and identified no novel nonsynonymous variants [50]. They did, however, report an association with the synonymous variant rs1052352, for which the C allele was more frequent in ET cases than controls (20.17% vs 12.32%; OR 1.64, 95% CI 1.23–2.18; P = 0.001), remaining significant following correction for multiple testing (50). The authors noted that this association had not been reproduced in previous studies and that its functional significance remained uncertain [50]. FUS remains a gene of interest, the available evidence does not establish rare FUS variants as a consistently replicated cause of ET, while the reported common-variant association requires independent validation.

Similarly, TENM4 was initially implicated through rare missense variants identified in three Spanish families. Yan et al. found no novel missense TENM4 variants and no significant association between ET and the three synonymous variants identified (rs11237621, rs689369 and rs2277277) [50]. These findings were consistent with an earlier negative Canadian study and did not support TENM4 as a general cause of ET in the Chinese population [50]. Taken together, the evidence suggests that reported TENM4 variants may be family/population-specific rather than representing a consistently replicated cause of ET [50].

4. DISCUSSION

This narrative review demonstrates substantial heterogeneity in the genetic evidence underlying ET. Across the 33 included studies/findings, common susceptibility loci, rare familial variants, repeat expansions and candidate-gene associations have been reported, but the strength of evidence supporting these findings varies considerably. Collectively, the literature supports a complex genetic architecture rather than a single major genetic cause of ET, while also highlighting persistent limitations in replication, phenotyping, ancestry representation and study size.

Interpretation of the genetic literature requires consideration of the strength and hierarchy of evidence rather than the number of reported genes or loci alone. Genome-wide studies with internal or independent replication provide stronger evidence for common susceptibility loci than isolated candidate-gene associations, while rare variants identified through familial sequencing require appropriate segregation, recurrence across additional families or cases, independent replication and/or functional evidence before a causal role can be inferred. Molecular diagnoses associated with an ET-like

phenotype should additionally be distinguished from susceptibility variants for ET itself. Consequently, not all genetic findings reported in ET have equivalent evidential weight.

4.1 GENETIC HETEROGENEITY AND REPLICATION

ET inheritance is not consistently autosomal dominant, and incomplete penetrance, age-dependent expression, variable expressivity and environmental influences contribute to complex patterns of familial aggregation [9, 23, 26]. Rare-variant studies included in this review frequently demonstrated incomplete or inconsistent segregation. With variants suggested by these studies often confined to individual families or identified in unaffected relatives or controls. Such findings do not rule out contribution to ET but substantially weakens their independent causality.

Most genetic studies in ET have lacked independent replication cohorts and have primarily been discovery studies. Although some studies have incorporated staged replication or attempted cross-population validation, reproducibility has remained limited. Discovery signals reproduced within a staged study design do not carry the same evidential strength as findings replicated in independent populations. Failure to replicate may reflect several factors, including false-positive initial associations, insufficient statistical power, differences in ancestry and allele frequency, phenotypic heterogeneity, or variation in diagnostic criteria between cohorts [9, 32].

This is particularly relevant to rare variants reported in genes such as TENM4, FUS, CACNA1G and SLIT3, where the supporting evidence has varied between studies and populations [13, 24, 26, 37]. Incomplete segregation, arising from factors such as age-dependent penetrance, phenocopies, variable expressivity or diagnostic uncertainty, further complicates assessment of replication. Co-segregation is therefore most informative when evaluating rare variants proposed to have large effects and should not be expected for common susceptibility alleles [9, 31]. Additional caution is required when interpreting variants in genes with established pathogenic associations with other neurological disorders. For example, pathogenic CACNA1G variants are associated with neurological phenotypes including spinocerebellar ataxia [13]. Rare CACNA1G variants identified in families with tremor should be interpreted cautiously, with consideration of subtle cerebellar features or an alternative tremor-predominant neurological disorder, rather than assumed to represent isolated ET [13].

Candidate-gene studies provide a further, generally weaker, tier of evidence. Associations have been reported across genes selected for their potential involvement in vitamin D metabolism, inflammation, oxidative stress, dopaminergic pathways and loci previously implicated in other neurological disorders [40–46]. However, many of these studies involved relatively small cohorts, hypothesis-driven selection of a limited number of variants, multiple statistical comparisons and little or no independent replication [40–47]. Overlap between candidate genes investigated in ET and genes associated with disorders such as PD should not itself be considered as evidence of shared genetic architecture [9, 32].

4.2 COMMON GENETIC SUSCEPTIBILITY

The emergence of larger GWAS has provided stronger evidence that common genetic variation contributes to ET susceptibility [33, 35]. However, individual common variants generally confer small effects and explain only a proportion of disease susceptibility [24, 33, 35]. Earlier associations involving LINGO1 and SLC1A2 have not been consistently replicated, highlighting the limited power of smaller genetic studies to reliably detect the modest effect sizes expected for common susceptibility variants [9, 35, 46].

More recent GWAS have identified additional loci [35, 39]. However, loci reaching genome-wide significance during discovery or with internal replication have less robust support than loci reproduced in independent cohorts. Signals reaching significance only in combined analyses require further validation and should not be considered comparable to independently replicated loci [32, 35].

Future GWAS should extend beyond the identification of individual associated genes or SNPs. Estimates of SNP-based heritability may help quantify the proportion of ET susceptibility attributable to measured common genetic variation [33]. Fine-mapping and functional annotation could be integrated to identify plausible causal variants, genes and biological pathways underlying association signals [32]. Genetic-correlation analyses could then examine whether ET shares components of its common genetic architecture with other neurological disorders. Evidence of such overlap should be established through appropriate genome-wide statistical analyses rather than inferred from similarities between individual candidate genes [32]. Larger and more ancestry-diverse cohorts are still required to provide sufficient power for these approaches [9, 33].

4.3 PHENOTYPIC HETEROGENEITY AND DISEASE CLASSIFICATION

ET remains a clinically defined syndrome rather than a molecularly defined disease, making phenotype definition particularly important when interpreting genetic associations. Changes in diagnostic classification over time

mean that cohorts assembled using different criteria may not represent directly comparable clinical populations.

A major challenge across both common- and rare-variant studies is the clinical definition of ET itself. Although most studies used established ET diagnostic criteria, 93.5% used frameworks that pre-dated the 2018 IPMDS classification, and only one study explicitly considered ET-plus [15]. Furthermore, formal longitudinal diagnostic reassessment was uncommon (9.7%). Consequently, differences in case definition and the potential inclusion of phenotypically heterogeneous or subsequently reclassified tremor syndromes may have contributed to variability between genetic cohorts. Misclassification may consequently weaken genuine genetic signals or generate apparent associations that cannot subsequently be reproduced.

Neuropathological findings provide a parallel example of this uncertainty. Post-mortem studies have failed to identify a common olivary pathology, with reported findings remaining widely debated and inconsistently reproduced [8, 10, 21, 22]. Reported Purkinje-cell loss and cerebellar torpedoes should be interpreted cautiously, as their consistency and specificity for ET remain uncertain, and some pathological changes may be age-related, secondary, or restricted to subsets of clinically diagnosed ET [2, 10, 19, 21, 51]. This variability could reflect biological heterogeneity within ET itself, methodological differences between studies or clinical misclassification, rather than representing established pathological subtypes of ET.

The identification of molecular diagnoses among individuals presenting with an ET-like phenotype further demonstrates the importance of precise phenotyping. Pathogenic GGC repeat expansions in NOTCH2NLC, reported in approximately 5–6% of selected East Asian familial ET cohorts, provide an important example. NOTCH2NLC expansions are associated with the heterogeneous neurodegenerative disorder neuronal intranuclear inclusion disease and may produce tremor among a wider spectrum of neurological manifestations [34, 39]. These findings could represent a molecularly defined subgroup or phenocopy within clinically diagnosed ET rather than establishing NOTCH2NLC as a general susceptibility gene for ET [34, 39]. The reported frequency should not be extrapolated beyond the ancestry and populations in which these studies were conducted until further evidence is found.

Greater consistency in diagnostic criteria and detailed documentation of age at onset, tremor distribution, family history and additional neurological features will be important for future genetic studies. Longitudinal phenotyping may be particularly valuable where initially isolated tremor subsequently evolves to include other neurological manifestations [15, 23].

4.4 CLINICAL IMPLICATIONS

Despite the increasing number of genetic variants and loci associated with ET, their current clinical utility remains limited. The heterogeneity of the evidence, small effect sizes of common susceptibility variants and limited replication of many rare and candidate-gene findings mean that genetic findings cannot currently be used reliably to confirm a diagnosis of typical ET, predict disease progression or guide treatment [26]. Genetic findings should be weighted according to the strength of their supporting evidence rather than the identification of a variant alone being considered evidence of causation.

Genetic investigation may have greater relevance where the clinical presentation is atypical or suggests an alternative inherited neurological disorder. Molecular diagnoses that may present with an ET-like phenotype, including pathogenic NOTCH2NLC repeat expansions in selected populations, highlight the importance of distinguishing disorders that mimic or overlap clinically with ET from genetic susceptibility to ET itself [34]. Additional neurological features or a strong or atypical family history may subsequently warrant consideration of an alternative genetic diagnosis where clinically appropriate.

At present, the principal potential clinical contribution of ET genetics is improved disease classification rather than prediction of individual outcomes. Better phenotyping combined with larger, ancestry-diverse genetic studies may help identify biologically meaningful subgroups within the broad clinical ET syndrome [13, 15]. Ultimately, integration of genetic findings with clinical, imaging and molecular data could improve diagnostic precision and identify biologically relevant therapeutic targets, but substantially stronger replication and validation are required before these approaches can be translated into routine clinical practice [23, 26].

4.5 EMERGING TECHNIQUES

4.5.1 Genetic and Molecular Approaches

The application of emerging genetic and molecular approaches, including long-read sequencing (LRS), polygenic risk scores (PRS) and multi-omics integration (MOI), could identify previously undetected genetic variation and clarify the biological pathways contributing to ET [36, 52, 53].

Long-read sequencing (LRS) may improve the detection and characterisation of repeat expansions, complex structural variants, mobile-element insertions and variants in difficult-to-sequence genomic regions, while also facilitating variant phasing [53]. The identification of pathogenic NOTCH2NLC GGC repeat expansions among patients presenting with ET-like phenotypes illustrates the

importance of investigating genetic variation beyond SNVs [34, 52]. However, the initial detection of repeat expansions using targeted methods such as repeat-primed PCR should be distinguished from their direct characterisation using LRS. Although these approaches may identify additional genetic variation in ET cohorts, there is currently insufficient evidence that repeat expansions or other complex variant classes account for a substantial proportion of typical ET. Larger, ancestry-diverse cohorts, independent replication and careful diagnostic assessment will be required to establish their contribution to ET susceptibility and distinguish ET-associated variation from molecular diagnoses presenting with ET-like tremor.

Medeiros et al. applied ET-derived PRS to investigate associations with brain structural phenotypes in approximately 30,000 UK Biobank participants [52]. Although such studies may help investigate relationships between common genetic susceptibility and neuroimaging phenotypes, an association with an imaging measure does not establish clinical predictive utility or define a biologically distinct ET subtype [52]. Current ET-derived PRS have not been sufficiently validated for individual risk prediction, family counselling or clinical subtyping. Further development will require larger discovery datasets, independent validation, assessment of predictive performance and evaluation across diverse ancestry groups.

MOI has recently been applied to ET to connect GWAS signals with gene expression and biological pathways. Yusufujiang et al. integrated GWAS data with transcriptome-wide association studies, gene-based analyses, eQTL data and spatial transcriptomics to prioritise 12 candidate genes for ET [54]. However, none showed significant differential expression in two independent post-mortem ET cerebellar datasets following correction for multiple testing [54]. This highlights the gap between computational gene prioritisation and biological validation and supports the need for larger, disease-relevant transcriptomic datasets to determine the functional significance of genetic associations. Current ET-specific multi-omics evidence remains limited, with computational prioritisation not yet consistently supported by disease-relevant experimental datasets. Integration of genomic data with larger ET-specific transcriptomic, proteomic and other molecular datasets may in future help identify convergent biological pathways, but the potential of these approaches currently exceeds the disease-specific evidence available [55].

4.5.2 Functional Approaches

Functional investigation remains essential for determining whether statistically associated or rare genetic variants have biological consequences relevant to ET. Cellular and animal models can investigate the effects of candidate variants on gene expression, protein function, neuronal signalling and cerebellar pathways [38, 55]. Existing experimental work in ET provides models for investigating mechanisms involving ion-channel function, GABAergic and glutamatergic signalling, and cerebellar oscillatory activity [55]. However, experimental models in which tremor is induced through pharmacological, optogenetic or other circuit manipulation should be distinguished from models directly incorporating human ET-associated genetic variants; the former provide evidence about potential disease mechanisms but do not independently validate specific human genetic associations. Such functional evidence is particularly important for rare variants identified in individual families, where genetic association and segregation alone may be insufficient to establish pathogenicity.

Future studies should therefore combine genetic discovery with replication, detailed phenotyping and targeted experimental validation. Rather than evaluating candidate genes in isolation, experiments guided by robust human genetic evidence may provide a stronger route towards identifying disease mechanisms and potential therapeutic targets.

4.6 LIMITATIONS AND FUTURE DIRECTIONS

The available literature remains limited by relatively small sample sizes, heterogeneous diagnostic criteria, differences in sequencing and analytical approaches, and under-representation of many ancestry groups. The inclusion of candidate-gene, familial sequencing and genome-wide studies also creates substantial methodological heterogeneity, preventing direct comparison of the strength of individual associations. As a narrative review, the present study additionally did not undertake formal meta-analysis or quantitative assessment of study quality, and the evidence hierarchy should thus be regarded as a framework for interpretation rather than a formal grading system.

Future research will require large, deeply phenotyped and ancestry-diverse cohorts with consistent diagnostic criteria. International collaboration will be particularly important for adequately powered GWAS and for replication of rare variants across independent families and populations. Greater availability of longitudinal phenotype data, genomic sequencing and complementary molecular data may subsequently allow genetic findings to be related to disease progression, clinical subtypes and treatment response.

4.7 CONCLUSION

The genetic landscape of ET remains complex and heterogeneous. Although genome-wide approaches

have strengthened evidence for common susceptibility loci, many rare and candidate-gene associations remain limited by small samples, incomplete segregation and inconsistent replication. Current evidence supports contributions from multiple forms of genetic variation but does not establish a single genetic model of ET. Better phenotyping, larger ancestry-diverse studies and integration with functional evidence will be important for determining which genetic findings have biological and ultimately clinical relevance.

ABBREVIATIONS

Autosomal dominant (AD), Candidate-gene case–control (CGCC), Copy number variation (CNV), Essential tremor (ET), Family based Linkage Studies (FBLS), Genome-wide association studies (GWAS), Long-read sequencing (LRS), Minor Allele Frequency (MAF), Multi-omics integration (MOI), Neuronal intranuclear inclusion disease (NIID), Parkinson's Disease (PD), Polygenic risk scoring (PRS), Single Nucleotide Polymorphism (SNP), Single Nucleotide Variant (SNV), Single-cell sequencing (SCS), Structural variants (SVs), Transcriptome-wide association analysis (TWAS), Whole-exome sequencing (WES), Whole-genome sequencing (WGS).

ADDITIONAL FILE

The additional file for this article can be found as follows:

- **Supplementary Data.** Supplementary data to this article can be found online at. DOI: https://doi.org/10.5334/tohm.1240.s1

COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHOR CONTRIBUTIONS

H. Shepherd-Macadie: Methodology & Original Draft.
D. Ledingham: Writing – Review & Editing.
J. Osman Farah: Writing – Review & Editing.
N. Pavese: Writing – Review & Editing.
A. Macerollo: Writing – Review & Editing, Conceptualization & Supervision.

AUTHOR AFFILIATIONS

Dr. Hilary Shepherd-Macadie orcid.org/0009-0000-9034-0161
School of Medicine, University of Liverpool, Liverpool, Liverpool L3 9TA, United Kingdom; The Walton Centre NHS Foundation Trust for Neurology and Neurosurgery, Liverpool, United Kingdom
Dr. David Ledingham orcid.org/0000-0002-6474-2666
Department of Neurosciences, Newcastle Upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; Clinical Ageing Research Unit, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, United Kingdom; Translational and Clinical Research Institute, The Medical School, Newcastle University, Newcastle upon Tyne, United Kingdom; NIHR Newcastle Biomedical Research Centre (BRC), Newcastle upon Tyne, United Kingdom
Mr. Jibril Osman Farah orcid.org/0000-0003-4359-8746
The Walton Centre NHS Foundation Trust for Neurology and Neurosurgery, Liverpool, United Kingdom
Dr. Nicola Pavese orcid.org/0000-0002-6801-6194
Department of Neurosciences, Newcastle Upon Tyne NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; Clinical Ageing Research Unit, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, United Kingdom; Translational and Clinical Research Institute, The Medical School, Newcastle University, Newcastle upon Tyne, United Kingdom; NIHR Newcastle Biomedical Research Centre (BRC), Newcastle upon Tyne, United Kingdom; Translational and Clinical Research Institute, Aarhus University Hospital Department of Nuclear Medicine & PET-Centre, Aarhus, Denmark
Prof. Antonella Macerollo orcid.org/0000-0003-4322-2706
The Walton Centre NHS Foundation Trust for Neurology and Neurosurgery, Liverpool, United Kingdom; Institute of Systems, Molecular and Integrative Biology, University of Liverpool, Liverpool, United Kingdom

REFERENCES

1. **Song P, Zhang Y, Zha M, Yang Q, Ye X, Yi Q,** et al. The global prevalence of essential tremor, with emphasis on age and sex: A meta-analysis. *J Glob Health.* 2021;11:04028. DOI: https://doi.org/10.7189/jogh.11.04028
2. **Louis ED, Ferreira JJ.** How common is the most common adult movement disorder? Update on the worldwide prevalence of essential tremor. *Mov Disord*. 2010;25(5):534–541. DOI: https://doi.org/10.1002/mds.22838
3. **Pan MK, Kuo SH.** Essential tremor: Clinical perspectives and pathophysiology. *J Neurol Sci.* 2022;435:120198. DOI: https://doi.org/10.1016/j.jns.2022.120198

4. **Hopfner F, Helmich RC.** The etiology of essential tremor: Genes versus environment. *Parkinsonism Relat Disord.* 2018;46Suppl 1:S92–S96. DOI: https://doi.org/10.1016/j.parkreldis.2017.07.014
5. **Ong YL, Deng X, Tan EK.** Etiologic links between environmental and lifestyle factors and Essential tremor. *Ann Clin Transl Neurol.* 2019;6(5):979–989. DOI: https://doi.org/10.1002/acn3.758
6. **Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Alvarez I, Pastor P, Agundez JAG.** Genomic Markers for Essential Tremor. *Pharmaceuticals (Basel).* 2021;14(6). DOI: https://doi.org/10.3390/ph14060516
7. **Jimenez-Jimenez FJ, Alonso-Navarro H, Garcia-Martin E, Lorenzo-Betancor O, Pastor P, Agundez JA.** Update on genetics of essential tremor. *Acta Neurol Scand.* 2013;128(6):359–371. DOI: https://doi.org/10.1111/ane.12148
8. **Hopfner F, Haubenberger D, Galpern WR, Gwinn K, Van't Veer A, White S,** et al. Knowledge gaps and research recommendations for essential tremor. *Parkinsonism Relat Disord.* 2016;33:27–35. DOI: https://doi.org/10.1016/j.parkreldis.2016.10.002
9. **Clark LN, Louis ED.** Challenges in essential tremor genetics. *Rev Neurol (Paris).* 2015;171(6–7):466–474. DOI: https://doi.org/10.1016/j.neurol.2015.02.015
10. **Louis ED.** Essential tremor: evolving clinicopathological concepts in an era of intensive post-mortem enquiry. *Lancet Neurol.* 2010;9(6):613–622. DOI: https://doi.org/10.1016/S1474-4422(10)70090-9
11. **Camargo CHF, Coutinho L, Zubko L, Franklin GL, Teive HAG.** The cerebellar involvement in essential tremor: the connecting roads. *Arq Neuropsiquiatr.* 2025;83(10):1–12. DOI: https://doi.org/10.1055/s-0045-1812324
12. **Okelberry T, Lyons KE, Pahwa R.** Updates in essential tremor. *Parkinsonism Relat Disord.* 2024;122:106086. DOI: https://doi.org/10.1016/j.parkreldis.2024.106086
13. **Odgerel Z, Sonti S, Hernandez N, Park J, Ottman R, Louis ED,** et al. Whole genome sequencing and rare variant analysis in essential tremor families. *PLoS One.* 2019;14(8):e0220512. DOI: https://doi.org/10.1371/journal.pone.0220512
14. **Louis ED.** Non-motor symptoms in essential tremor: A review of the current data and state of the field. *Parkinsonism Relat Disord.* 2016;1(01):S115–S118. DOI: https://doi.org/10.1016/j.parkreldis.2015.08.034
15. **Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED.** Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society. *Mov Disord.* 2018;33(1):75–87. DOI: https://doi.org/10.1002/mds.27121
16. **Louis ED, Bares M, Benito-Leon J, Fahn S, Frucht SJ, Jankovic J.** Essential tremor-plus: a controversial new concept. *Lancet Neurol.* 2020;19(3):266–270. DOI: https://doi.org/10.1016/S1474-4422(19)30398-9
17. **Espay AJ, Lang AE, Erro R, Merola A, Fasano A, Berardelli A.** Essential pitfalls in "essential" tremor. *Mov Disord.* 2017;32(3):325–331. DOI: https://doi.org/10.1002/mds.26919
18. **Louis ED.** Essential tremor: a nuanced approach to the clinical features. *Pract Neurol.* 2019;19(5):389–398. DOI: https://doi.org/10.1136/practneurol-2018-002183
19. **Louis ED.** Linking Essential Tremor to the Cerebellum: Neuropathological Evidence. *Cerebellum.* 2016;15(3):235–242. DOI: https://doi.org/10.1007/s12311-015-0692-6
20. **Helmich RC, Toni I, Deuschl G, Bloem BR.** The pathophysiology of essential tremor and Parkinson's tremor. *Curr Neurol Neurosci Rep.* 2013;13(9):378. DOI: https://doi.org/10.1007/s11910-013-0378-8
21. **Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA.** Neuropathological changes in essential tremor: 33 cases compared with 21 controls. *Brain.* 2007;130(Pt 12):3297–3307. DOI: https://doi.org/10.1093/brain/awm266
22. **Louis ED, Vonsattel JP.** The emerging neuropathology of essential tremor. *Mov Disord.* 2008;23(2):174–182. DOI: https://doi.org/10.1002/mds.21731
23. **Siokas V, Aloizou AM, Tsouris Z, Liampas I, Aslanidou P, Dastamani M,** et al. Genetic Risk Factors for Essential Tremor: A Review. *Tremor Other Hyperkinet Mov (N Y).* 2020;10:4. DOI: https://doi.org/10.5334/tohm.67
24. **Clark LN, Gao Y, Wang GT, Hernandez N, Ashley-Koch A, Jankovic J,** et al. Whole genome sequencing identifies candidate genes for familial essential tremor and reveals biological pathways implicated in essential tremor aetiology. *EBioMedicine.* 2022;85:104290. DOI: https://doi.org/10.1016/j.ebiom.2022.104290
25. **Kovach MJ, Ruiz J, Kimonis K, Mueed S, Sinha S, Higgins C,** et al. Genetic heterogeneity in autosomal dominant essential tremor. *Genetics in medicine.* 2001;3(3):197–199. DOI: https://doi.org/10.1097/00125817-200105000-00009
26. **Diez-Fairen M, Houle G, Ortega-Cubero S, Bandres-Ciga S, Alvarez I, Carcel M,** et al. Exome-wide rare variant analysis in familial essential tremor. *Parkinsonism Relat Disord.* 2021;82:109–116. DOI: https://doi.org/10.1016/j.parkreldis.2020.11.021
27. **Deuschl G, Petersen I, Lorenz D, Christensen K.** Tremor in the elderly: Essential and aging-related tremor. *Mov Disord.* 2015;30(10):1327–1334. DOI: https://doi.org/10.1002/mds.26265
28. **Louis ED.** Essential tremor then and now: How views of the most common tremor diathesis have changed over time. *Parkinsonism Relat Disord.* 2018;46 Suppl 1(Suppl 1):S70–S74. DOI: https://doi.org/10.1016/j.parkreldis.2017.07.010
29. **Louis ED, Dogu O.** Does age of onset in essential tremor have a bimodal distribution? Data from a tertiary referral setting and a population-based study. *Neuroepidemiology.* 2007;29(3–4):208–212. DOI: https://doi.org/10.1159/000111584

30. **Louis ED.** The Essential Tremors: Evolving Concepts of a Family of Diseases. *Front Neurol.* 2021;12:650601. DOI: https://doi.org/10.3389/fneur.2021.650601
31. **Bailey-Wilson JE, Wilson AF.** Linkage analysis in the next-generation sequencing era. *Hum Hered.* 2011;72(4):228–236. DOI: https://doi.org/10.1159/000334381
32. **Visscher PM, Wray NR, Zhang Q, Sklar P, McCarthy MI, Brown MA.** 10 Years of GWAS Discovery: Biology, Function, and Translation. *Am J Hum Genet.* 2017;101(1):5–22. DOI: https://doi.org/10.1016/j.ajhg.2017.06.005
33. **Liao C, Castonguay CE, Heilbron K, Vuokila V, Medeiros M, Houle G.** Association of Essential Tremor With Novel Risk Loci: A Genome-Wide Association Study and Meta-analysis. *JAMA Neurol.* 2022;79(2):185–193. DOI: https://doi.org/10.1001/jamaneurol.2021.4781
34. **Sun QY, Xu Q, Tian Y, Hu ZM, Qin LX, Yang JX.** Expansion of GGC repeat in the human-specific NOTCH2NLC gene is associated with essential tremor. *Brain.* 2020;143(1):222–233. DOI: https://doi.org/10.1093/brain/awz372
35. **Muller SH, Girard SL, Hopfner F, Merner ND, Bourassa CV, Lorenz D.** Genome-wide association study in essential tremor identifies three new loci. *Brain.* 2016;139(Pt 12):3163–3169. DOI: https://doi.org/10.1093/brain/aww242
36. **Liao C, Sarayloo F, Rochefort D, Houle G, Akcimen F, He Q,** et al. Multiomics Analyses Identify Genes and Pathways Relevant to Essential Tremor. *Mov Disord.* 2020;35(7):1153–1162. DOI: https://doi.org/10.1002/mds.28031
37. **Orsucci D, Tessa A, Caldarazzo Ienco E, Trovato R, Natale G, Bilancieri G.** Clinical and genetic features of dominant Essential Tremor in Tuscany, Italy: FUS, CAMTA1, ATXN1 and beyond. *J Neurol Sci.* 2024;460:123012. DOI: https://doi.org/10.1016/j.jns.2024.123012
38. **Hor H, Francescatto L, Bartesaghi L, Ortega-Cubero S, Kousi M, Lorenzo-Betancor O,** et al. Missense mutations in TENM4, a regulator of axon guidance and central myelination, cause essential tremor. *Hum Mol Genet.* 2015;24(20):5677–5686. DOI: https://doi.org/10.1093/hmg/ddv281
39. **Yau WY, Vandrovcova J, Sullivan R, Chen Z, Zecchinelli A, Cilia R.** Low Prevalence of NOTCH2NLC GGC Repeat Expansion in White Patients with Movement Disorders. *Mov Disord.* 2021;36(1):251–255. DOI: https://doi.org/10.1002/mds.28302
40. **Agundez JAG, Garcia-Martin E, Alonso-Navarro H, Rodriguez C, Diez-Fairen M, Alvarez I.** Vitamin D Receptor and Binding Protein Gene Variants in Patients with Essential Tremor. *Mol Neurobiol.* 2022;59(6):3458–3466. DOI: https://doi.org/10.1007/s12035-022-02804-8
41. **Sazci A, Uren N, Idrisoglu HA, Ergul E.** The rs2228570 Variant of the Vitamin D Receptor Gene is Associated with Essential Tremor. *Neurosci Bull.* 2019;35(2):362–364. DOI: https://doi.org/10.1007/s12264-018-0287-6
42. **Chen J, Huang P, He Y, Shen J, Du J, Cui S.** IL1B polymorphism is associated with essential tremor in Chinese population. *BMC Neurol.* 2019;19(1):99. DOI: https://doi.org/10.1186/s12883-019-1331-5
43. **Ayuso P, Agundez JAG, Alonso-Navarro H, Martinez C, Benito-Leon J, Ortega-Cubero S.** Heme Oxygenase 1 and 2 Common Genetic Variants and Risk for Essential Tremor. *Medicine (Baltimore).* 2015;94(24):e968. DOI: https://doi.org/10.1097/MD.0000000000000968
44. **Chao YX, Ng EY, Tan L, Prakash KM, Au WL, Zhao Y.** Lrrk2 R1628P variant is a risk factor for essential tremor. *Sci Rep.* 2015;5:9029. DOI: https://doi.org/10.1038/srep09029
45. **Yuan L, Deng X, Song Z, Deng S, Zheng W, Mao P.** Systematic analysis of genetic variants in patients with essential tremor. *Brain Behav.* 2018;8(10):e01100. DOI: https://doi.org/10.1002/brb3.1100
46. **Jimenez-Jimenez FJ, Garcia-Martin E, Alonso-Navarro H, Lorenzo-Betancor O, Ortega-Cubero S, Pastor P.** A family study of DRD3 rs6280, SLC1A2 rs3794087 and MAPT rs1052553 variants in essential tremor. *Neurol Res.* 2016;38(10):880–887. DOI: https://doi.org/10.1080/01616412.2016.1210355
47. **Ortega-Cuberoa S, Lorenzo-Betancor O, Lorenzo E, Agúndeze JAG, Jimenez-Jimenez FJ, Ross OA, Wurster I, Mielke C, Lin J-J, Coria F, Clarimonc J, Ezquerra M, Brighinam L, Annesi G, Alonso-Navarro H, García-Martin E, Gironell A, Marti MJ, Yueh K-C, Wszolek ZK, Sharma M, Berg D, Krüger R, Pastor MA, Pastor P.** TREM2 R47H variant and risk of essential tremor: a cross-sectional international multicenter study. *Parkinsonism Relat Disord.* 2015;21(3):306–309. DOI: https://doi.org/10.1016/j.parkreldis.2014.12.010
48. **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. *Nat Genet.* 2009;41(3):277–279. DOI: https://doi.org/10.1038/ng.299
49. **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. *Am J Hum Genet.* 2012;91(2):313–319. DOI: https://doi.org/10.1016/j.ajhg.2012.07.002
50. **Yan YP, Xu CY, Gu LY, Zhang B, Shen T, Gao T,** et al. Genetic testing of FUS, HTRA2, and TENM4 genes in Chinese patients with essential tremor. *CNS Neurosci Ther.* 2020;26(8)(1755–5949 (Electronic)):837–841. DOI: https://doi.org/10.1111/cns.13305
51. **Louis ED, Faust PL, Ma KJ, Yu M, Cortes E, Vonsattel JP.** Torpedoes in the cerebellar vermis in essential tremor cases vs. controls. *Cerebellum.* 2011;10(4):812–819. DOI: https://doi.org/10.1007/s12311-011-0291-0

52. **Medeiros M, Pastor-Bernier A, Azizi H, Schmilovich Z, Castonguay CE, Savadjiev P.** Brain Imaging Phenotypes Associated with Polygenic Risk for Essential Tremor. *Mov Disord.* 2025;40(6):1160–1171. DOI: https://doi.org/10.1002/mds.30167
53. **Marsili L, Duque KR, Bode RL, Kauffman MA, Espay AJ.** Uncovering Essential Tremor Genetics: The Promise of Long-Read Sequencing. *Front Neurol.* 2022;13:821189. DOI: https://doi.org/10.3389/fneur.2022.821189
54. **Yusufujiang A, Zeng S, Xu L, Li G, Wang Z, Li H.** Integrative Multi-Omics Analysis Prioritizes Candidate Genes for Essential Tremor and Reveals a Gap Between Computational Prediction and Experimental Validation. *Mov Disord.* 2026;41(2):351–360. DOI: https://doi.org/10.1002/mds.70101
55. **Aboasali F, Castonguay CE, Medeiros M, Dion PA, Rouleau GA.** Tremor in the Age of Omics: An Overview of the Transcriptomic Landscape of Essential Tremor. *Cerebellum.* 2025;24(2):35. DOI: https://doi.org/10.1007/s12311-025-01793-3

TO CITE THIS ARTICLE:
Shepherd-Macadie H, Ledingham D, Osman Farah J, Pavese N, Macerollo A. The Genetic Architecture of Essential Tremor. *Tremor and Other Hyperkinetic Movements.* 2026; 16(1): 64, pp. 1–14. DOI: https://doi.org/10.5334/tohm.1240

Submitted: 25 May 2026 **Accepted:** 31 October 2026 **Published:** 17 November 2026

COPYRIGHT:
© 2026 The Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See https://creativecommons.org/licenses/by/4.0/.

Tremor and Other Hyperkinetic Movements is a peer-reviewed open access journal published by Ubiquity Press.