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Genetics of essential tremor: From phenotype to genes, insights from both human and mouse studies

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ABSTRACT

Essential tremor (ET) is a prevalent neurological disorder of unknown etiology characterized by the presence of an action tremor that occurs during voluntary motion and affects primarily the upper limbs. The worldwide prevalence of the disease in the general population is 0.9%, increasing to 4.6% in individuals ≥65 years old. Standard pharmaceutical treatments are only moderately effective, reducing tremor amplitudes in ~50% of patients, a phenomenon partly explained by the fact that the diagnosis of ET is based solely on clinical findings rather than biological markers. Furthermore, the pathophysiological origin of ET remains controversial, leading to heated debates as to whether it should be considered a neurodegenerative disorder or as a dynamic oscillatory disturbances of neurologic origin. Progress has been made in the understanding of its etiology as it is now accepted that genetic components must at least explain the familial cases of ET, and the evidence implicating the olivocerebellar and cerebello-thalamo-cortical pathways is strong. However, a strong disconnection between human genetics, pathophysiological, and mouse genetics studies exists in the field of ET, with little use of all the knowledge gathered from the different research disciplines. This review highlights our current knowledge on ET from both a human population and mouse genetics perspective hoping to reconcile evidence from both fields and leading to novel clues guiding future studies. We argue that better communication between researchers of different fields is warranted to define the biological origin of ET in the hope of leading to the development of better treatments.

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Abbreviations: ABA, Allen brain atlas; AβPPswe/PS1ΔE9, amyloid-β protein precursor and presenilin-1; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ATP, adenosine tri-phosphate; BAC, bacterial artificial chromosome; *BDNF*, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; cM, centiMorgan; CNS, central nervous system; CSF, cerebrospinal fluid; CTX, cerebral cortex; DN, dentate nuclei; *DRD3*, dopamine receptor D3; EAE, experimental autoimmune encephalomyelitis; ENCODE, encyclopedia of DNA elements; ET, essential tremor; *ETM1-4*, hereditary essential tremor 1–4; FGFR1, fibroblast growth factor receptor-1; fMRI, functional magnetic resonance imaging; *FUS/TLS*, fused in sarcoma/translocated in liposarcoma; $GABA_A$, gamma-aminobutyric acid-$_a$; $GABA_B$, gamma-aminobutyric acid-$_b$; GLT-1, glutamate transporter 1; GWAS, genome wide association study; HEK293, human embryonic kidney 293; *HS1BP3*, hematopoietic-specific protein 1 binding protein 3; HuGX, human genes on the X-chromosome; Hz, Hertz; IKMC, knockout mouse consortium; IO, inferior olive; ION, inferior olive neurons; LB, Lewy bodies; LC, locus coeruleus; LID, levodopa-induced dyskinesia; *LINGO1*, leucine rich repeat and Ig domain containing 1; MAPK, mitogen-associated protein kinase; MCR, minimal critical region; MDS, movement disorder society; mGluR5, metabotropic glutamate group receptor 5; MIP, molecular inversion probe; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; MS, multiple sclerosis; NAA, *N*-acetyl-L-aspartate; NES, nuclear export signal; NLS, nuclear localization signal; NMDAR, n-methyl-D-aspartate receptor; OR, odd ratio; 6-OHDA, 6-hydroxydopamine; PC, Purkinje cells; PD, Parkinson's disease; PET, positron emission tomography; RhoA, ras homolog member A; SC, spinal cord; *SLC1A2*, solute carrier family 1 – glial affinity glutamate transporter – member 2; STR, striatum; TFIID, transcription factor II D; TH, thalamic nuclei; TRIG, Tremor Investigation Group; WHIGET, Washington Heights-Inwood Genetic Study of Essential Tremor; 14-3-3Θ, tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein theta polypeptide.

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1. Background on essential tremor

Essential tremor (ET) is a prevalent neurological disorder of unknown etiology that was first described by Pietro Burresi in 1874 (Louis et al., 2008). The disease is characterized by the presence of an action tremor that occurs during voluntary motion and affects primarily the upper limbs (Deuschl et al., 1998). Although non-life threatening, ET can be the cause of social embarrassment as well as functional impairments. The worldwide prevalence of the disease in the general population is 0.9%, increasing to 4.6% in individuals ≥65 years old (Louis and Ferreira, 2010). A review of the literature shows an exponential increase in PubMed entries related to ET over the second half of the 20th century, with 1309 entries for the 2001–2010 period (Fig. 1A). Looking at the recent yearly number of PubMed entries, this trend is clearly continuing (Fig. 1B). These results demonstrate an increasing interest for ET and the desire of the medical and scientific community to better understand its pathology. It has long been known that genetic factors are important for ET, with four loci identified: three using linkage studies – hereditary essential tremor 1 (*ETM1*) [OMIM 190300], *ETM2* [OMIM 602134], *ETM3* [OMIM 611456], – and a fourth locus identified using exome sequencing, *ETM4* [OMIM 614782]. However, to date, no causative mutations in a gene have been reproducibly reported in ET. Standard pharmaceutical treatments are only moderately effective, reducing tremor amplitudes in ~50% of patients (Chen and Swope, 2003), a phenomenon partly explained by the fact that the diagnosis of ET is based solely on clinical findings rather than biological markers. The disease is thought to be highly heterogeneous, which partly explain the low efficacy of the current treatments. Furthermore, the pathophysiological origin of ET remains controversial, leading to heated debates as to whether it should be considered a neurodegenerative disorder or occurs as dynamic oscillatory disturbances of neurologic origin (Deuschl and Elble, 2009). This reality highlights a need for additional research to be conducted in order to improve our understanding of this complex disorder with the objective of developing better treatments. Novel drugs discovery for effective ET treatment will require a better understanding of its cause (Blair et al., 2008; Deng et al., 2005; Higgins et al., 2005; Jeanneteau et al., 2006; Merner et al., 2012; Parmalee et al., 2013). Future research should continue to focus on both human population and pathophysiology studies, but should also include development of novel appropriate animal models for ET. This review highlights our current knowledge on ET from both a human population and mouse genetics perspective hoping to reconcile evidence from both fields and leading to novel clues guiding future studies.

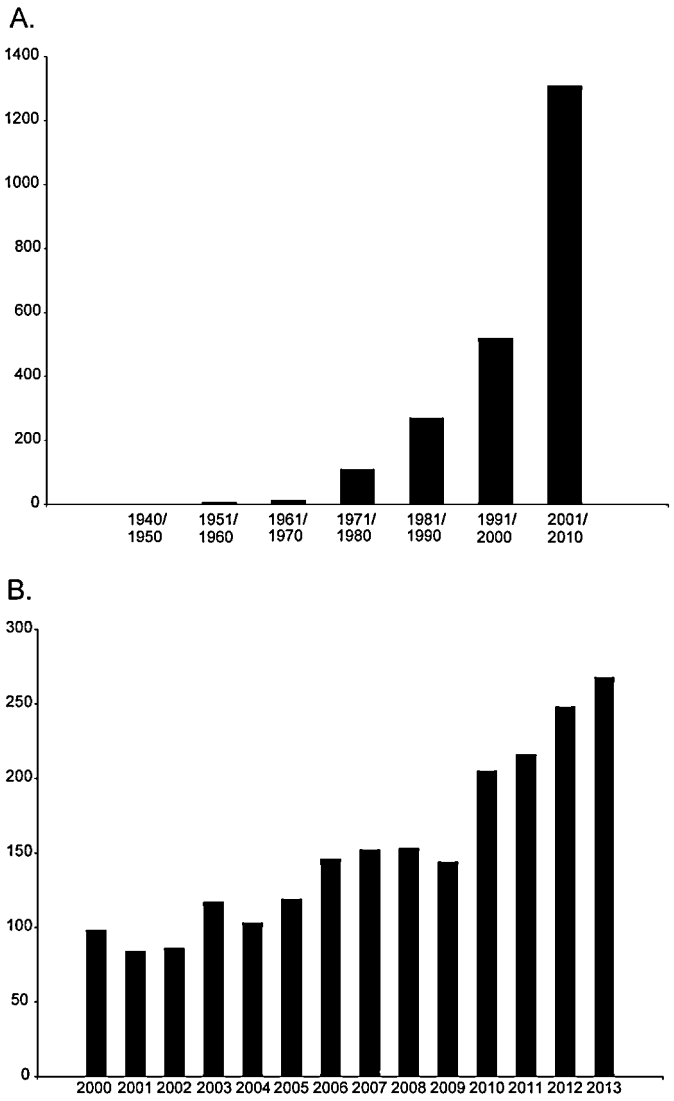

Fig. 1. Scientific interest in essential tremor has progressively increased over the past decades. (A) Interrogation of the PubMed literature database (http://www.ncbi.nlm.nih.gov/pubmed) revealed an exponential growing body of literature in essential tremor from 1940 to 2010. (B) Similarly, the growing body of literature in essential tremor progressively increased over the past decade (2000–2013). Search terms for Essential Tremor were interrogated in "all fields" per year.

2. Essential tremor: the disease

ET is the second most prevalent adult-onset movement disorder after restless legs syndrome, and one of the most prevalent neurological disorders (Louis and Ferreira, 2010; Nomura et al., 2008; Tison et al., 2005). To date, no clear physiological or biological markers exist that are specific to ET, so the diagnosis is based only on clinical observations. Typically the diagnosis of ET is based on criteria established by one of three different organizations; the Tremor Investigation Group (TRIG), the Movement