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Essential tremor: genetic update

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Abstract

Essential tremor (ET) is a neurological movement disorder characterised by bilateral limb kinetic/postural tremor, with or without tremor in other body parts including head, voice and lower limbs. Since no causative genes for ET have been identified, it is likely that the disorder occurs as a result of complex genetic factors interacting with various cellular and environmental factors that can result in abnormal function of circuitry involving the cerebello–thalamo–cortical pathway. Genetic analyses have uncovered at least 14 loci and 11 genes that are related to ET, as well as various risk or protective genetic factors. Limitations in ET genetic analyses include inconsistent disease definition, small sample size, varied ethnic backgrounds and many other factors that may contribute to paucity of relevant genetic data in ET. Genetic analyses, coupled with functional and animal studies, have led to better insights into possible pathogenic mechanisms underlying ET. These genetic studies may guide the future development of genetic testing and counselling, and specific, pathogenesis-targeted, therapeutic strategies.

Introduction

Essential tremor (ET) is a common movement disorder with reported prevalence of approximately 1% in the worldwide population (Ref. 1). The age at onset appears to have a bimodal distribution with peaks around 2nd decade and 6th decade of life (Ref. 2). The original consensus statement of the Movement Disorder Society on tremor described the inclusion criteria of classic ET as follows: (i) bilateral, mostly symmetric postural or kinetic tremor, involving in hands and forearms and (ii) additional or isolated tremor involving in head, without abnormal posturing (Ref. 3). Although there is no agreement among experts how to define ET, recent Movement Disorders Society 'consensus' statement proposed that ET is a syndrome with the following diagnostic criteria: (i) isolated tremor syndrome of bilateral upper limb action tremor; (ii) at least 3 years' duration; (iii) with or without tremor in other locations (e.g. head, voice or lower limbs) and (iv) the absence of other neurological signs, such as dystonia, ataxia or parkinsonism (Ref. 4). Some patients start with ET syndrome but may later evolve into another tremor syndrome, such as Parkinson's disease (PD) (Ref. 4). Such patients with ET–PD combinations have been classified as patients with PD and 'antecedent ET', but the relationship between the two disorders is not fully understood (Ref. 5).

Another controversy in the field of ET is whether it is a chiefly physiological disorder resulting in abnormal function of the basal ganglia, thalamus, cerebellum and other structures or whether it is a neurodegenerative disorder. There is a growing support for the notion that the pathogenesis of ET is partly related to loss of Purkinje cells (PCs) and other pathological cerebellar abnormalities along with reduced γ-aminobutyric acid (GABA) receptor expression in the dentate nucleus (Ref. 6). Additionally, neurodegenerative changes such as Lewy bodies (LBs) reported in brains of some ET patients suggest the overlap between ET and PD (Refs 5–7).

Although family history was thought not to be consistent enough to be included in the ET definition by the consensus statement (Ref. 4), it is well recognised that genetic factors play a major role in ET pathogenesis. ET is familial in about 50–70% of cases (Ref. 8). First-degree relatives of ET patients were reported to have 4.7-fold risk of developing ET compared with controls (Ref. 9). In twin studies, pairwise concordance was approximately two times in monozygotic twins, compared with dizygotic twins (Ref. 10). It has been proposed that ET is inherited as a complex disorder requiring interactions of genetic and non-genetic factors, but alternative explanations including polygenic inheritance and mitochondrial origin cannot be excluded (Ref. 11). At least 14 loci and 11 disease-causing genes related to ET have been described in the literature and reported in the Online Mendelian Inheritance in Man (OMIM, http://omim.org/) (Refs 6, 12, 13) (Table 1 and Fig. 1). In addition, many more genetic variants have been reported as risk or protective factors of ET, though the findings have been inconsistent (Refs 6, 14, 15) (Fig. 1).

Although no ET-specific gene mutations have yet been identified, there is great interest in genetic testing in families with ET. In one study, 90/105 (85.7%) of families with ET expressed interest in being tested for possible genetic abnormalities (Ref. 16). In this review we provide insights into possible genetic mechanisms of this common neurological disorder (Fig. 2),

Table 1. Summary of gene loci and disease-causing genes associated with essential tremor

Loci/ genes	OMIM	Location on chromosome	Author	References	Sample size	Ethnicity or geography distribution	Inheritance model	Candidate gene or mutation analysis	Remarks
ETM1	190300	3q13	Gulcher *et al.*	17	16 families	Iceland	AD	No	Identification of *ETM1*
			Kovach *et al.*	28	1 family	Midwestern America	AD	No	Exclusion of linkage to *ETM1*
			Illarioshkin *et al.*	19	4 families	Tajik	AD	No	Confirmation of *ETM1*
			Jeanneteau *et al.*	20	30 families	French	AD or polygenic	*DRD3*-coding sequence and the first 871 bp of the 5' flanking region	*DRD3*-Ser9Gly variant may be a risk factor of ET
					276 ET patients, 184 controls	America	AD or polygenic	*DRD3*-Ser9Gly variant	
			Ma *et al.*	29	4 families	-	AD or polygenic?	*DRD3*-Ser9Gly variant	Exclude the causation of *DRD3*-Ser9Gly variant
			Tan *et al.*	22	163 ET patients, 192 controls	Asians		*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant is unlikely to be a risk factor of ET
			Blair *et al.*	23	433 ET patients, 272 controls	Caucasians		*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant is not associated with ET
			Inashkina *et al.*	24	104 ET patients and 116 controls	Latvia		*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant is not associated with ET
			Vitale *et al.*	25	116 ET patients, 158 controls	Italy		*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant is not associated with ET
			Aridon *et al.*	30	1 family	Italy	AD	No	Exclusion of linkage to *ETM1*
			García-Martín *et al.*	21	201 ET patients, 282 controls	Spain		*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant may be associated with the risk of ET
			Lorenz *et al.*	26	202 familial cases, 97 non-familial ET patients, 528 controls and 22 ET families	Germany, Denmark and France	AD or polygenic	*DRD3*-Ser9Gly variant	*DRD3*-Ser9Gly variant is not associated with ET
			Novelletto *et al.*	27	4 ET families	Italy	AD	No	Exclusion of linkage to *ETM1*
ETM2	602134	2p24.1	Higgins *et al.*	35	1 family	American kindred of Czech ancestry	AD	No	Mapping of *ETM2*
			Higgins *et al.*	36	3 families	America	AD	No	Supporting the linkage to *ETM2*
			Higgins *et al.*	37	45 ET patients and 70 controls	White		No	Supporting the linkage to *ETM2*
			Higgins *et al.*	41	52 ET patients, 49 controls	Singapore		No	Supporting the linkage to *ETM2*
			Kim *et al.*	38	30 sporadic ET patients, 30 controls	Korea		No	Supporting the linkage to *ETM2*

			Higgins *et al.*	39	21 families, 150 controls	America	AD	2 genes and 7 transcripts in the 464 kb region between loci *D2S2150* and *etm1231*	*HS1BP3* A265G variant may be associated with familial ET
			Deng *et al.*	40	222 familial ET patients, 132 controls 1 family	North America	AD	*HS1BP3* A265G variant	The *HS1BP3* A265G variant is not associated with ET
			Kovach *et al.*	28	1 family	Midwestern America	AD	No	Exclusion of linkage to *ETM2*
			Ma *et al.*	29	4 families	America	AD and polygenic?	No	Exclusion of linkage to *ETM2*
			Aridon *et al.*	30	1 family	Italy	AD	No	Exclusion of linkage to *ETM2*
			Novelletto *et al.*	27	4 ET families	Italy	AD	No	Exclusion of linkage to *ETM2*
ETM3	611456	6p23	Shatunov *et al.*	42	1 family	North America	AD or polygenic	*TBCID7*, *GFOD1*, *SIRT5*, *NOL7*, *RANBP9*, *LOC441130*, *C6orf79*, *PHACTR1*, *JARID2*, *DTNBP1*, *MYLIP*, *GMPR*, *SCA1*, *CAP2*, *NHLRC1*	Mapping of *ETM3*
			Aridon *et al.*	30	1 family	Italy	AD	No	Exclusion of linkage to *ETM3*
			Novelletto *et al.*	27	4 ET families	Italy	AD	No	Exclusion of linkage to *ETM3*
FUS (*ETM4*)	137070 (614782)	16p11.2	Merner *et al.*	43	1 ET family and 270 ET cases	Canada	AD	Exome sequencing for the ET family, the *FUS* gene for 270 ET cases	*FUS* p.Q290* was identified as the genetic cause of an ET family, and no other causal variants were found *FUS* p.P431L and p.R216C were found to be associated with ET in ET cohort
			Zheng *et al.*	45	180 ET patients, 273 controls	Han-Chinese		*FUS* coding region and exon-intron boundaries	*FUS* p.M392I was found to be associated with ET in ET cohort
			Parmalee *et al.*	47	259 ET patients, 262 controls	North America		All exons of *FUS* in 116 early-onset ET cases, 4 SNPs in all samples	No mutation or risk factor found
			Ortega-Cubero *et al.*	48	178 ET patients	Spanish		The *FUS* gene	No definite mutation found
			Hedera *et al.*	49	104 ET patients from 52 pedigrees	Caucasians	AD	*FUS* coding sequence	No definite mutation found
			Labbé *et al.*	53	152 familial ET cases, 112 sporadic ET patients and 716 controls	Non-Hispanic Caucasians of mixed European ancestry		All exons of *FUS* in familial cases, 3 reported variants in sporadic cases and controls	No definite mutation found
			Rajput *et al.*	46	217 ET patients, 219 controls	Canada		Entire *FUS* coding sequence in ET patients, 2 variants in controls	*FUS* p.R377W was found to be associated with ET in ET cohort
TENM4 (*ETM5*)	610084 (616736)	11q14.1	Hor *et al.*	58	3 families, additional 297 familial ET cases	Europeans of Spanish origin	AD	WES study for a family, *TENM4* targeted resequencing for 299 ET cases	*TENM4* p.T1367N was identified in all affected individuals in an ET family, *TENM4* targeted resequencing respectively found p.A1442T and p.V1138M in 2 ET families

(*Continued*)

Table 1. (*Continued.*)

Loci/ genes	OMIM	Location on chromosome	Author	References	Sample size	Ethnicity or geography distribution	Inheritance model	Candidate gene or mutation analysis	Remarks
			Chao *et al.*	59	379 ET patients, 398 controls	Chinese		*TENM4* p.A1442T	*TENM4* p.A1442T was found in none of ET patients but two asymptomatic healthy individuals
HTRA2	606441	2p13.1	Unal Gulsuner *et al.*	64	1 ET family	Turkish	AD	WES study for 3 family members, *HTRA2* p.G399S for all family members	*HTRA2* p.G399S was identified as the genetic cause of an ET family by WES study, and no other causal variants were found
			Tzoulis *et al.*	66	204 PD patients, 103 ET patients, 72 tremulous cervical dystonia cases and 29 nontremulous cervical dystonia cases	Norway		*HTRA2* p.G399S	*HTRA2* p.G399S was found in 2 PD patients, which does not support the association between *HTRA2* p.G399S and ET
			Chao *et al.*	67	468 ET patients, 778 PD patients, 14 ET/PD patients and 517 controls	Asians		*HTRA2* p.G399S	*HTRA2* p.G399S was found in a healthy control, and it seems to be not associated with ET or PD
			He *et al.*	65	101 familial ET patients, 105 familial PD patients, 15 ET/PD patients and 100 controls	Chinese		Coding region and exon-intron boundaries of *HTRA2*	*HTRA2* p.G399S seems to be not associated with ET or PD
SCN4A	603967	17q23.3	Bergareche *et al.*	72	1 ET family and 76 sporadic, 47 familial patients	Spanish	AD	WES study in an ET family, *SCN4A* coding region in 22 familial ET cases, *SCN4A* p.G1537S in 76 sporadic, 25 familial ET cases	*SCN4A* p.G1537S was identified as a disease-segregating mutation in an ET family by WES study, and no other causal variants were found
SORT1	602458	1p13.3	Sánchez *et al.*	76	1 family with early-onset ET, 151 ET cases, 188 control chromosomes	Spanish	AD	WES study for 4 family members, *SORT1* coding region in 61 ET cases and *SORT1* exon 4 in 90 ET cases	*SORT1* p.G171A was identified as a disease-segregating mutation in the ET family by WES study, and no other causal variants were found
SCN11A	604385	3p22.2	Leng *et al.*	12	1 family with early-onset episodic pain and adult-onset ET	Chinese	AD	WES for the proband, co-segregated analysis of *SCN11A* p.R225C in family members	*SCN11A* p.R225C was identified in a large ET family by WES study, and no other causal variants were found
NOS3	163729	7q36.1	Liu *et al.*	13	37 early-onset ET families	-	AD	WES for at least 2 affected individuals from each of 37 families, co-segregated analysis of *NOS3* p.G16S and p.P55L in the 2 families	*NOS3* p.G16S and p.P55L were identified to be cosegregated with ET in 2 families by WES studies, and no other causal variants were found in the 2 families

KCNS2	602906	8q22.2	Liu *et al.*	13	37 early-onset ET families and 95 ET cases	-	AD	WES for at least 2 affected individuals from each of 37 families, co-segregated analysis of *KCNS2* p.D379E in the family and *KSCN2* coding region in 95 ET cases	*KCNS2* p.D379E was identified in the ET family by WES study, and no other causal variants were found in the family, and no *KSCN2* variants in 95 ET cases
HAPLN4	-	19p13.11	Liu *et al.*	13	37 early-onset ET families	-	AD	WES for at least 2 affected individuals from each of 37 families, co-segregated analysis of *HAPLN4* p.G350R in the family	*HAPLN4* p.G350R was identified in the ET family by WES study, and no other causal variants were found in the family
USP46	612849	4q12	Liu *et al.*	13	37 early-onset ET families	-	AD	WES for at least 2 affected individuals from each of 37 families, co-segregated analysis of *USP46* p.A133V in the family	*USP46* p.A133V was identified in the ET family by WES study, and no other causal variants were found in the family
CACNA1G	604065	17q21.33	Clark	Lorraine Clark, personal communication	3 ET families	-			Whole genome sequence and WES studies identified 'functional' variants in *CACNA1G*

AD, autosomal dominant; ET, essential tremor; PD, Parkinson's disease; SNP, single-nucleotide polymorphism; WES, whole exome sequence.

which, we hope, will lead to better diagnosis and novel treatment discoveries in future research of ET.

Genetic loci and gene analysis for ET

We define 'variant' is a neutral term including 'mutation' and 'polymorphism'. The term 'nucleotide mutation', usually used in monogenic disorders, describes disease-causing or apparently disease-associated sequence variation. The term 'polymorphism', usually used in polygenic diseases, describes non-disease-causing sequence variation that has a frequency of at least 1% in the population (Ref. 11). We use 'variant' when it is not certain whether the sequence variation is a highly penetrant risk or is a confirmed risk factor for the disease.

Essential tremor 1 (ETM1, *OMIM 190300*)

ETM1, located on chromosome 3q13, was first found to be linked with ET by genome-wide scan of 16 Icelandic families in 1997 (Ref. 17), and subsequently supported by findings in the Tajik families (Refs 18, 19). A p.S9G variant in the dopamine receptor D3 gene (*DRD3*) located in *ETM1* was reported to confer inheritable susceptibility to ET in 23 French families (Ref. 20) and in early-onset Caucasian patients from Spain (Ref. 21). However, follow-up studies in Asian, Latvian, Italian, German, Danish, French and other populations with ET were not able to confirm this genetic susceptibility (Refs 22–30). Therefore, based on these irreproducible results, the *DRD3* gene may, at best, be considered as a minor factor in ET susceptibility (Ref. 25).

A possible relationship has been found between dopamine D3 receptor (DRD3) and ET. DRD3, encoded by the *DRD3* gene, usually highly expresses in the basal ganglia, and also expresses in the cerebellum, which has been implicated in the ET pathogenesis (Ref. 20). In rat, DRD3 has been found to be expressed in the rat cerebellar PCs (Ref. 31). Several studies have provided support for the hypothesis that dysfunction in the cerebello–thalamo–cortical pathway played a role in the pathogenesis of ET, suggesting the expression level of *DRD3* may be related to ET (Ref. 32). *DRD3* may be implicated in some neurologic movement disorders including PD and tardive dyskinesia (Refs 33, 34), but further research is needed to better define the relationship between *DRD3* and ET.

Essential tremor 2 (ETM2, *OMIM 602134*)

ETM2 was mapped to a 15-cM candidate region on chromosome 2p22-p25 in a Czech-American ET family in 1997 (Ref. 35). In a follow-up analysis adding three additional American families with ET, *ETM2* was delimited to a 9.1-cM interval between the loci *D2S224* and *D2S405* by haplotype reconstruction (Ref. 36). In 2003, a haplotype on chromosome 2p24.1 formed by *etm1231* and *etm1234* was found to be segregated with ET (Ref. 37). Further analysis of *ETM2* candidate region on chromosome 2p24.1 in Korean ET patients supports the linkage between *ETM2* and ET (Ref. 38). In 2005, the p.A265G variant (828C>G) in the HCLS1 binding protein 3 gene (*HS1BP3*), located in the minimal critical region (MCR) of *ETM2*, was reported as the causal variant in two unrelated ET families from America (Ref. 39). However, the p.A265G variant was not found to cosegregate with ET in a large Caucasian family in our study (Ref. 40). Four recombination events were found in the <1 cM region between *D2S2150* and *etm1234*, challenging the *ETM2* MCR (Ref. 11). Reviewing previous studies, *ETM2* may be mapped near the 9.1-cM interval between *D2S224* and *D2S405* (Refs 35–41), and the p.A265G variant in the *HS1BP3* gene is probably not responsible for monogenic ET (Ref. 40).

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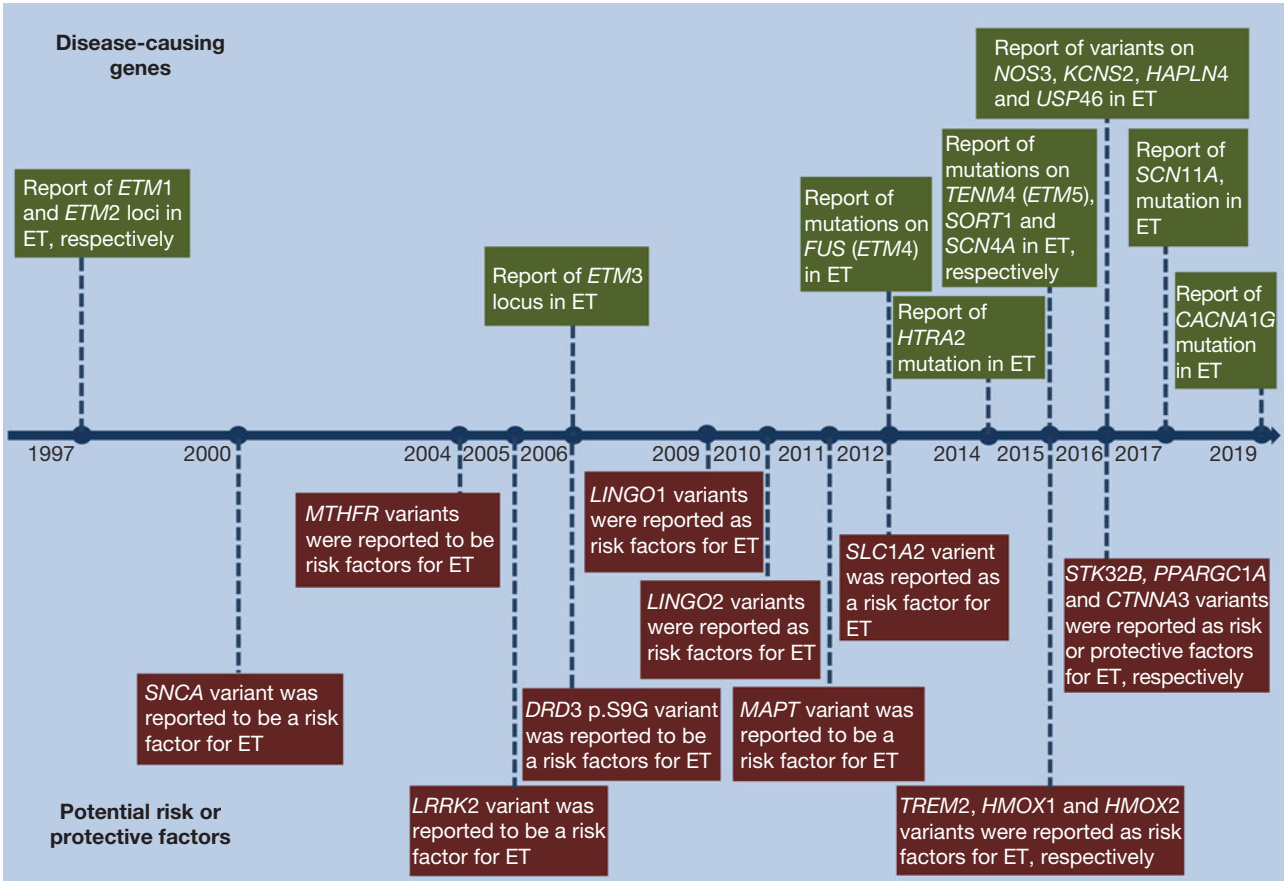

Fig. 1. Milestones in essential tremor research of disease-causing genes and potential risk or protective factors. The horizontal arrow in the middle of the figure represents the timeline. Disease-causing genes are shown above the timeline and potential risk or protective factors are shown below the timeline.

*Essential tremor 3 (*ETM3, *OMIM 611456)*

In 2006, Shatunov *et al*. mapped the *ETM3* locus to chromosome 6p23 by a combination of genome-wide linkage screening and fine mapping, but no pathogenic variant was identified after sequencing of 15 genes located in candidate regions (Ref. 42). Given that the disease-associated haplotype was not present in some definite ET patients, and individuals harbouring the disease-associated haplotype didn't have fully developed ET in these families (Ref. 42), a low penetrance or a high phenocopy rate should be considered in ET genetic expression if there is a monogenic causal gene in *ETM3* (Ref. 2).

*The FUS RNA binding protein gene (*FUS, *OMIM 137070) and essential tremor 4 (*ETM4, *OMIM 614782)*

In 2012, p.Q290* mutation in the *FUS* gene on chromosome 16p11.2 was described to be responsible for ET by exome sequencing in a large ET-affected family (*ETM4*) (Refs 43, 44). Another two variants, p.P431L and p.R216C, were identified in this gene by screening additional 270 ET patients (Ref. 43). Further screening in our 180 Chinese Han patients detected a *FUS* p.M392I mutation (Ref. 45). Furthermore, a *FUS* p.R377W mutation was found by screening 217 Canadian cases (Ref. 46). However, the linkage between *FUS* and ET could not be replicated in other studies. No causal mutation was observed in 116 early-onset ET cases from America (Ref. 47) or several other cohorts (Refs 48, 49), and *FUS* might be a very rare cause of ET.

Although the exact function of the FUS protein is not clear, FUS appears to play a role in a series of cellular processes, including DNA repair, transcription regulation, cell proliferation, as well as RNA and microRNA processes (Ref. 50). Even though *FUS* mutations may be a rare cause of ET, specific cellular and nervous system functions may be impaired by *FUS* mutations, possibly leading to loss of FUS function and development of ET (Refs 43, 51). FUS has two structural parts: nuclear localisation signal (NLS) and nuclear export signal (NES) sequences5, which play an important part in the nucleus–cytoplasm shuttle (Ref. 51). The ET-related *FUS* mutation has been reported to be located in the NES motif, possibly interfering with FUS export from nucleus to cytoplasm via the nuclear pore complex (Ref. 43). *FUS* mutations are also known to possibly cause other neurological disorders including amyotrophic lateral sclerosis (ALS) (Ref. 52). The ET-causing mutations may be located in the NES and its transcripts are degraded by the nonsense-mediated-decay pathway (Ref. 53), whereas the ALS-causing mutations usually disrupt the NLS and lead to a truncated protein product (Refs 52, 53).

Multiple animal models, including *Drosophilae*, zebrafish and mice, have provided powerful tools in studying the role of FUS loss-of-function in neurodegeneration. *Drosophilae* with human *FUS*-Q290* (*hFUS*-Q290*) may show specific characteristics that can be found in ET patients including age-related motor dysfunction, linked to the impairment of GABA-ergic pathway (Ref. 54). In zebrafish, expression of mutant *FUS* or knock-down *fus* leads to locomotor impairment, and the *fus*-knock-down dysfunction can be rescued through co-expression of wild-type (WT) *hFUS* (Refs 55, 56). In mice, $Fus^{-/-}$ mice showed lymphocyte reduction and short survival time, but $Fus^{+/-}$ mice showed phenotypes undifferentiated from $Fus^{+/+}$ animals (Ref. 57).

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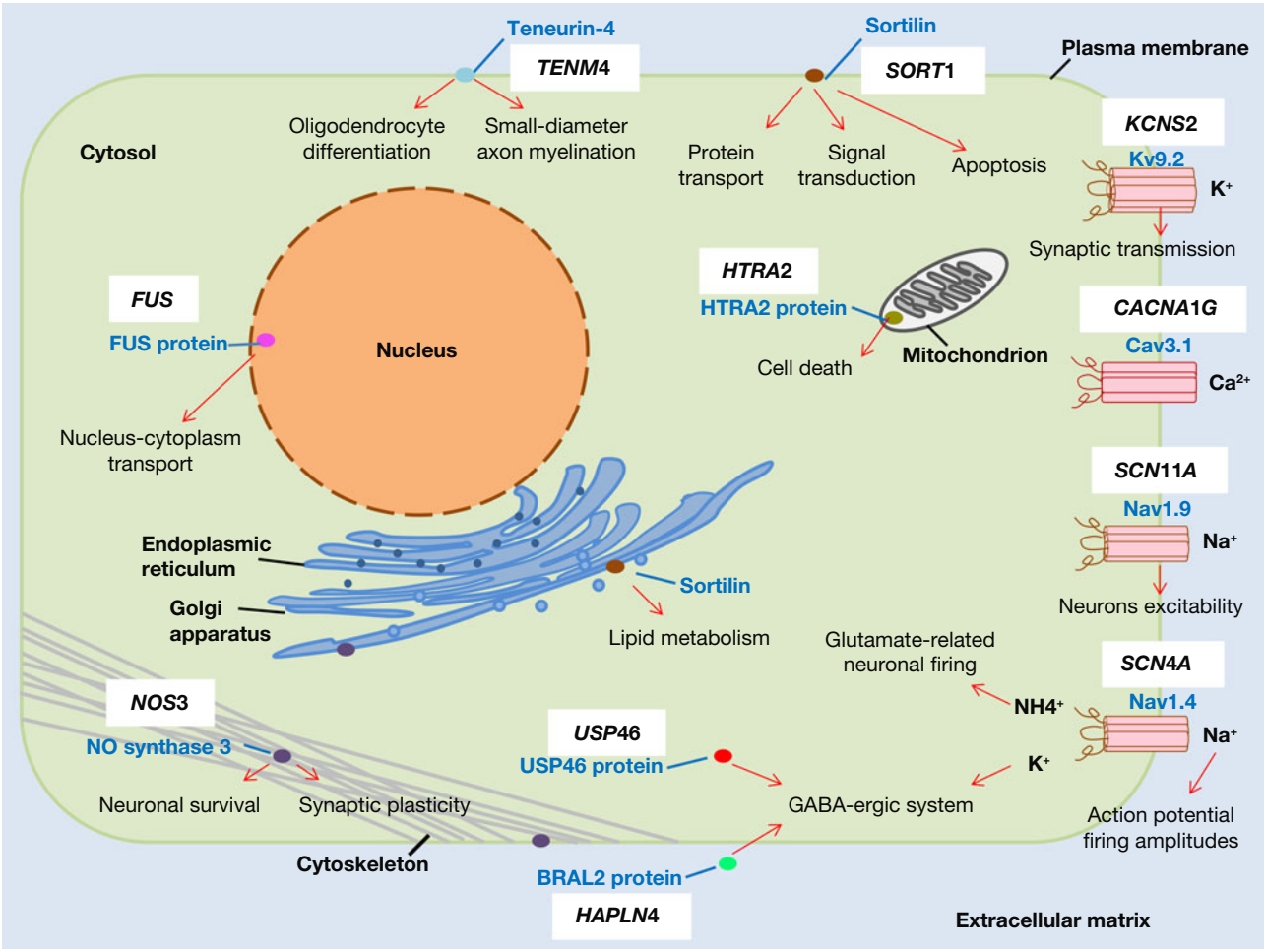

Fig. 2. An illustration of subcellular location and proposed function of gene products associated with essential tremor. FUS protein usually locates in nucleus and regulates nucleus–cytoplasm transport. *TENM4* product, teneurin-4, was reported to enable its localisation to plasma membrane, and involved in neural development. HTRA2 protein, found in mitochondrion intermembrane space, promotes or induces cell death. Sortilin (*SORT1* product), a protein usually regulating lipid metabolism, was found in plasma membrane and promotes neuronal apoptosis. Products of *SCN4A* and *SCN11A* mediate the voltage-dependent sodium ion permeability and membrane excitability, and products of *KCNS2* can form functional heterotetrameric channels with KCNB1 and KCNB2, modulating the voltage-gated potassium channel activation then synaptic transmission. *CACNA1G* affects the calcium channel and 'functional' variants were recently found in ET families. NO synthase 3 (*NOS3* product), highly expressed in cytoskeleton, plasma membrane and Golgi apparatus, was reported to participate in neuronal survival and synaptic plasticity. USP46 protein probably located in cytosol and BRAL2 protein (*HAPLN4* product) located in extracellular matrix, regulate GABA action. GABA, γ-aminobutyric acid.

*The teneurin transmembrane protein 4 gene (*TENM4*, OMIM 610084), essential tremor 5 (*ETM5*, OMIM 616736)*

In 2015, disease-segregated mutations in the *TENM4* gene mapped to chromosome 11q14.1 was identified in some Spanish ET families by whole exome sequence (WES) study (*ETM5*) (Ref. 58). However, the previously described *TENM4* p.A1442T mutation (Ref. 58), was not found in any of 379 Chinese ET cases (but was found in two healthy individuals), suggesting that further studies of this variant are needed in larger ET cohorts and different populations (Ref. 59).

TENM4, a member of the teneurin gene family, is highly expressed in the nervous system, and has been found to encode signalling molecule that functions as type-II transmembrane receptor at the cellular surface, or as a transcriptional regulator after intracellular domain export (Ref. 60). *TENM4* can regulate oligodendrocyte differentiation, and affect the small-diameter axon myelination in the central nervous system (CNS) (Ref. 61). In mice, *Tenm4* expression was found in the white matter of the cerebellum (Ref. 62). *In vitro* study with Oli-neu cells showed that the *TENM4* mutations contribute to a TENM4 protein mislocalisation, from homogeneous membrane localisation to wrong-clustered localisation (Ref. 58). This may hinder the TENM4-mediated phosphorylation and affect the oligodendroglial process outgrowth (Ref. 58).

Synapse loss, as well as impairment in general synapse organisation and target select regulation was observed in *Drosophilae* with teneurin perturbations (Ref. 63). In transfected zebrafish, suppression and overexpression of *TENM4* mRNA lead to defective branching and extension in the small diameter axon involving in truncal musculature (Ref. 58). Tremors were only observed in $Tenm4^{-/-}$ transgene mice but not in $Tenm4^{+/-}$ mice (Ref. 61). This suggests the possibility that the WT allele in heterozygous mice upregulates the Ten-4 expression and plays a compensating action (Ref. 61). Tremor phenotype was presented in $Tenm4^{-/-}$ mice, and its severity may reflect the dominant-negative effect of mutant *TENM4* between haploinsufficiency and null phenotype (Refs 58, 61). In $Tenm4^{-/-}$ mice, especially in the central nervous system (CNS) spinal cord, myelination was dramatically reduced in small-diameter axons, and oligodendrocyte differentiation was inhibited (Ref. 61).

*The HtrA serine peptidase 2 gene (*HTRA2*, OMIM 606441)*

In 2014, a p.G399S mutation (c.1195G>A) in the *HTRA2* gene was reported to be the causative mutation for ET in a

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six-generation Turkish family (Ref. 64). Compared with heterozygotes, patients with homozygous *HTRA2* p.G399S were linked to earlier age at onset and, severe postural/kinetic tremor with development of PD in the middle age (Ref. 64). It should be noted that other groups, however, did not find the association between *HTRA2* p.G399S and ET development in populations from Asian and Norway (Refs 65–67).

The *HTRA2* gene, located on chromosome 2p13 (Ref. 68), codes for *HTRA2*, a serine protease located in mitochondrial intermembrane space (Ref. 69). It can be released into cytosol through an apoptotic stimulus and bind to the inhibitor of apoptosis proteins, initiating apoptosis (Refs 64, 69). The *HTRA2* p.G399S mutation was reported to change the mitochondrial morphology and function, reduce the protease activity and increase sensitivity to toxicity (Ref. 70). WT *HtrA2* over-expressed mice showed a worse motor behavioural phenotype than *HtrA2* p.G399S over-expressed mice, suggesting that *HTRA2* p.G399S has a dominant-negative effect (Ref. 71).

The sodium voltage-gated channel alpha subunit 4 gene (SCN4A, OMIM 603967)

In 2015, a p.G1537S mutation in the *SCN4A* gene was found to be segregated with ET in a large Spanish family by WES study (Ref. 72). *SCN4A*, mapped to chromosome 17q23.1-q25.3 (Ref. 73), was generally considered as a muscle-specific gene, playing a major role in the pathogenesis of primarily myopathic disorders (Refs 72, 74). It encodes the voltage-sensitive sodium channel (Nav1.4) protein that was also confirmed in the human cerebral cortex, suggesting the *SCN4A* expression in neuronal tissues (Ref. 72). *SCN4A* p.G1537S mutation is situated in the IVS5-S6 loop portion, which inserts into the membrane and constructs the pore lining, playing an important role in ion selectivity of the sodium channel (Ref. 72). Whole-cell patch-clamp studies showed a faster activation and a significantly faster near-threshold potential inactivation of channels with p.G1537S mutation, which could alter ion selectivity, reduce the repetitive action potential firing amplitudes, increase neural membrane excitability and accelerate the thalamic oscillations that manifest as tremor (Refs 72, 75). In addition, increased potassium and ammonium conductance was found in mutant protein, which may be involved in cortical inhibition impairment, causing neurological dysfunction and seizure activity (Ref. 72).

The sortilin 1 gene (SORT1, OMIM 602458)

In 2015, a disease-segregating mutation p.G171A was identified in the *SORT1* gene in a Spanish family with early-onset ET (Ref. 76). *SORT1*, located on chromosome 1p13 (Ref. 77), encodes sortilin, which is a member of the cellular vacuolar protein sorting 10 domain receptor family expressed in both CNS and peripheral nervous system (PNS) neurons (Ref. 76). Sortilin acts as a neurotensin receptor, and plays a role in protein transport and signal transduction, regulating the viability and function of neurons (Refs 78, 79). It can also interact with the p75 neurotrophin receptor ($p75^{NTR}$) and contribute to proNGF- and proBDNF-induced apoptosis of neurons (Ref. 76). It has been reported that loss of sortilin activities may be associated with the development of several nervous system disorders including Alzheimer disease (Ref. 79). The *SORT1* p.G171A mutation reduced both mRNA and protein level of *SORT1* whereas the expression of its binding partner $p75^{NTR}$ was increased, which may cause abnormalities in neurotransmission deficiency and possibly tremor (Ref. 76).

The sodium voltage-gated channel alpha subunit 11 gene (SCN11A, OMIM 604385)

In 2017, a p.R225C mutation in the *SCN11A* gene was identified in a four-generation Chinese family with early-onset episodic pain and adult-onset ET (Ref. 12). *SCN11A*, located on chromosome 3p22.2, primarily expresses in the PNS nociceptors, and encodes Nav1.9 (Ref. 12). The voltage-sensitive Na^+ channels usually act as transmembrane proteins that play roles in action potential generation of excitable cells (Ref. 80). Nav1.9 regulates excitability of resting neurons by depolarising prolongation of subthreshold stimulus (Refs 12, 81, 82).

The nitric oxide synthase 3 gene (NOS3, OMIM 163729)

In 2016, variants p.G16S and p.P55L in the *NOS3* gene were reported to be cosegregated with ET in two early-onset ET families, respectively (Ref. 13). Further replicated results are needed to confirm the association between *NOS3* and ET. *NOS3*, located on 7q36 (Ref. 83), encodes a major NO synthase isoform that highly expresses in the cerebellum, and plays a part in neurotransmitter NO conversion that affects NO-mediated neuronal survival and synaptic plasticity (Refs 13, 84). The NOS pathway has been reported to be involved in the development of several neurological disorders including PD and Alzheimer disease (Refs 84, 85).

The potassium voltage-gated channel modifier subfamily S member 2 gene (KCNS2, OMIM 602906)

In 2016, a *KCNS2* heterozygous p.D379E variant was reported to probably be the causal variant in an early-onset ET family by WES study, but subsequent Sanger sequencing on *KCNS2* in additional 95 unrelated ET cases did not find any mutations (Ref. 13). Follow-up replications are needed to confirm that association.

KCNS2 (KV9.2), encoded by the *KCNS2* gene, is a K^+ channel α subunit that is highly expressed in the cerebellar PCs and granular cells, and modulates both KV2.1 and KV2.2 channel activities (Refs 13, 86). KCNS2 may regulate resting membrane potential and control the shape and frequency of action potentials (Ref. 86). This is supported by the similar function of *Drosophila Shab*, a highly homologous gene to *KCNS2*, regulating repetitive synaptic activities (Ref. 87). Mutations in *Drosophila Shaker*, which interacts with *Drosophila Shab* in synaptic transmission regulation, resulted in motor circuit abnormality, increased neuromuscular junction neurotransmission and leg shaking of *Drosophilae* under etherisation (Refs 13, 88), supporting the notion that K^+ channel abnormities may be involved in ET pathology. Additionally, patients with mutant voltage-gated potassium channel gene (*KCNA1*, *KV1.1*), another member of K^+ channel family, showed a tremor phenotype (Refs 89, 90).

The hyaluronan and proteoglycan link protein 4 gene (HAPLN4)

In one family with an early-onset ET, a p.G350R variant was reported as a probable causal variant in the *HAPLN4* gene (Ref. 13). Repetitive studies are required for confirmation. *HAPLN4* is mainly expressed in GABA-ergic neurons including PCs and basket neurons in the cerebellar cortex (Ref. 91). Tremor has been linked to cerebellar neurodegeneration that was accompanied by PC loss, reduced activity of GABA system in deep cerebellar neurons, output disinhibition of deep cerebellar neurons that have pacemaker activity and the enhanced rhythmic activity of the thalamo-cortical circuit and thalamus (Ref. 92).

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The ubiquitin specific peptidase 46 gene (USP46, OMIM 612849)

A heterozygous variant p.A133V in the *USP46* gene was reported to be cosegregated with ET in an early-onset ET family, by WES study (Ref. 13). Follow-up studies are needed for replication. *USP46* is a deubiquitinating enzyme that is highly expressed in the cerebellum (Refs 13, 93), which can regulate multilevel cellular functions by dissociating ubiquitin from protein substrates (Ref. 94). Impaired function of deubiquitinating enzyme family has been reported to lead to some neurodegenerative diseases such as PD (Ref. 95), but not bipolar disorder and schizophrenia (Ref. 96). Mutant or knock-out *Usp46* in mice have been found to have impaired regulation of GABA-ergic system, implicated in the pathophysiology of ET (Refs 97–99).

The calcium voltage-gated channel subunit alpha1 G gene (CACNA1G, OMIM 604065)

Whole genome sequence and WES studies have recently identified 'functional' variants in the calcium voltage-gated channel subunit alpha1 G gene (*CACNA1G*, Cav3.1) in three ET families (Clark L., personal communication). Electrophysiologic studies by whole cell patch clamp recordings in HEK293T cells expressing the Cav3.1 mutant channels showed significant differences in the gating of the mutant Cav3.1 channels compared with the WT channel. Further studies are needed to confirm the sensitivity and specificity of this finding in populations of patients with ET, but T-type calcium channel modulators have been proposed to be effective in the treatment of ET (Ref. 100).

Genetic risk or protective factors of ET

In addition to searching for monogenic causes of ET, genetic risk or protective factors also should be considered in the effort to better understand the pathogenesis of the disease.

The leucine rich repeat and Ig domain containing 1 gene (LINGO1, OMIM 609791)

In 2009, two ET-risk variants, rs9652490 and rs11856808, were reported in the *LINGO1* gene by genome-wide association study (GWAS) of 452 Icelandic ET patients, and these variants were then found to have association with ET in follow-up samples from the United States, Germany, Austria and Iceland (Ref. 101). Other subsequent studies, however, obtained incongruous results (Refs 102–109). Intriguingly, whole-genome single-nucleotide polymorphism microarray analysis identified a genomic duplication encompassing the *LINGO1* gene as the likely cause of familial dystonic tremor in a South Indian family recently (Ref. 110), indicating that copy number variants (CNVs) may play an important role in the development of ET.

The *LINGO1* gene, mapped to chromosome 15q24 (Ref. 111), encodes a transmembrane glycoprotein specific to the CNS (Ref. 112). It is highly expressed in neocortex, hippocampus, thalamus, amygdale and expressed in cerebellum and basal nuclei at lower levels (Ref. 113). The LINGO1 protein is involved in regulating neuronal survival, oligodendrocyte differentiation, axonal outgrowth and regeneration with a negative manner. Over-expression of LINGO1 has been found in the ET cerebellar cortex, and it appears to play a role in PC degeneration (Ref. 114). CNS axonal myelination was found to develop earlier, and axonal integrity was improved in knock-out *Lingo1* mice, with no obvious abnormalities of behaviour compared with WTs (Ref. 115).

The leucine rich repeat and Ig domain containing 2 gene (LINGO2, OMIM 609793)

Variants rs1412229, rs7033345 and rs10812774 in the *LINGO2* gene, a paralogue of *LINGO1*, were found to confer increased susceptibility for ET (Refs 106, 116).

In mice, the LINGO2 protein was found in the brain and seems to be restricted to neuronal tissue (Refs 117, 118). Owing to the high homology, LINGO2 may present similar functions as LINGO1 and play an important role in maintenance of dopaminergic integrity (Ref. 116).

The solute carrier family 1 member 2 gene (SLC1A2, OMIM 600300)

In 2012, variant rs3794087 in the *SLC1A2* gene was reported to be associated with ET susceptibility by GWAS of 990 cases and 1537 controls from Europe (Ref. 119). However, this variant appeared to be related to ET protection in a Chinese cohort (Ref. 120), suggesting that linkage disequilibrium exists in different races, and rs3794087 is only a genetic marker reflecting *SLC1A2* or its nearby gene associated with ET susceptibility.

The *SLC1A2* gene, located on chromosome 11p13-p12 (Ref. 121), primarily encodes a glial high-affinity glutamate reuptake transporter called 'excitatory amino acid transporter type 2' (EAAT2) in the brain (Refs 119, 122). EAAT2 is expressed around the PC axon initial segment. In ET cases, EAAT2 is significantly reduced in cerebellar cortex (Ref. 122). EAAT2 function is to protect glutamatergic olivo-cerebellar climbing fibres from excitotoxic injury, which can lead to PC excitotoxic death, postulated to be involved in ET pathogenesis (Refs 51, 122). *Slc1a2*$^{-/-}$ mice showed high susceptibility of acute cortical injury in the brain, as well as epilepsy (Ref. 123).

The serine/threonine kinase 32B gene (STK32B)

In 2016, GWAS in 2807 European patients and 6441 controls found that C allele of rs10937625 in the *STK32B* gene acts as a protective factor of ET (Ref. 15). This positive result was replicated by analysis of 218 cases and 315 controls of Han Chinese population (Ref. 124).

The *STK32B* gene, located on chromosome 4p16 (Ref. 125), encodes the serine/threonine kinase. The *STK32B* expression, which was increased in ET cerebellar cortex, was found to be reduced with the rs10937625 variant, located on the DNase hypersensitive place of *STK32B*, supporting possible protective role of the rs10937625 C allele in development of ET (Refs 15, 124).

The PPARG coactivator 1 alpha gene (PPARGC1A, OMIM 604517)

The rs17590046 variant in the *PPARGC1A* gene was found to be related to the susceptibility of ET by GWAS (Ref. 15). However, conflicting results were described in two independent studies in Asian populations (Refs 124, 126).

The *PPARGC1A* gene, located on chromosome 4p15.1 (Ref. 127), encodes a transcriptional coactivator called the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which plays a role in mitochondrial function and energy metabolism (Ref. 15). PGC-1α can regulate oxidative metabolism and oxidative capacity-associated biological programmes, and loss of PGC-1α function may result in neuronal degeneration in the brain, especially in the striatum (Ref. 128). Altered-function of PGC-1α has been reported to be associated with several neurodegenerative movement disorders including PD and Huntington's disease (HD), which share similar $GABA_A$

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receptor abnormality as described in ET (Refs 129–131). Motor impairment and striatal vacuolation are found in knocked-out PGC-1α mice, suggesting that PGC-1α plays an important role in motor function (Ref. 132).

The catenin alpha 3 gene (CTNNA3, OMIM 607667)

The rs12764057, rs10822974 and rs7903491 variants in the *CTNNA3* gene were reported to be associated with ET susceptibility by GWAS in European patients (Ref. 15). Subsequently, the G allele of the *CTNNA3* rs7903491 variant was confirmed as an ET risk factor whereas the association of ET for rs12764057 and rs10822974 could not be duplicated in a Chinese cohort (Ref. 124).

CTNNA3, located on chromosome 10q21 (Ref. 133), encodes a cell–cell adhesion molecule named catenin alpha 3 (Ref. 15), which is primarily expressed in testis and heart, with lower expression in the brain (Ref. 134). *CTNNA3* has been reported to be involved in Alzheimer disease development (Ref. 135), though the specific pathogenic pathway is not clear. There is some epidemiological evidence for possible clinical and pathological overlap between ET and Alzheimer disease, but further studies are needed to establish the link (Refs 51, 136).

Risk factors associated with other neurological diseases

ET phenotype has been reported to possibly overlap with other neurological diseases including PD, Alzheimer disease, HD, ALS, dystonia and myoclonus (Refs 11, 51, 52, 131). These reported associations have been challenged, but research into possible genetic causes of ET and related neurological diseases may provide new insights into the relationship between ET and other diseases.

Based on many epidemiologic and other studies, the support for ET–PD relationship is stronger than the other associations (Ref. 137). In addition, pathologic studies have found LB pathology in brains of ET patients (Ref. 7), providing additional support for the relationship between ET and PD. A variety of variants on genes that are related to PD have been reported as risk factors for ET susceptibility, including the synuclein alpha gene (*SNCA*) (Ref. 138), the leucine rich repeat kinase 2 gene (*LRRK2)* (Ref. 139), the methylenetetrahydrofolate reductase gene (*MTHFR*) (Ref. 140), the heme oxygenase 1 gene (*HMOX1*), the heme oxygenase 2 gene (*HMOX2*) (Ref. 141), the microtubule associated protein tau gene (*MAPT*) (Ref. 142) and the triggering receptor expressed on myeloid cells 2 gene (*TREM2*) (Ref. 143).

ET-like tremor was also found in X-linked spinal and bulbar muscular atrophy, type 1 (SMAX1, also known as Kennedy disease), fragile X tremor/ataxia syndrome (FXTAS), spinocerebellar ataxia type 12 (SCA-12) and some other neurological diseases (Ref. 11). Variants in the related genes such as the androgen receptor gene (*AR*) (Ref. 144), the fragile X mental retardation 1 gene (*FMR1*) (Ref. 145), the protein phosphatase 2 regulatory subunit β gene (*PPP2R2B*, also known as *SCA12*), the peripheral myelin protein 22 gene (*PMP22*), the chromosome 9 open reading frame 72 gene (*C9orf72*), the ataxin 2 gene (*ATXN2*), and the ataxin 3 gene (*ATXN3*) may shed light on ET genetic risk factors (Ref. 2). However, abnormalities in these genes have not been consistently found in ET population studies and their pathogenic relationship to ET, if any, is doubtful.

Genetic factors suggested by animal models

Animal models provide important insights into the pathogenesis of ET and may contribute to the development of treatment. Reduced GABA levels in the cerebrospinal fluid of ET patients (Ref. 146), as well as the well-recognised tremor suppression by alcohol and other GABA-ergic drugs including benzodiazepines, suggests that the disturbed GABA-ergic pathway may play a role in ET pathogenesis (Refs 147, 148). Postural/kinetic tremor and motor incoordination, which are characteristics of ET, were reported in $GABA_A$ receptor $\alpha 1^{-/-}$ (*Gabra1*$^{-/-}$) mice (Refs 149, 150), but no susceptibility association has been found after genetic analysis of the gamma-aminobutyric acid type A receptor alpha1 subunit gene (*GABRA1*) in ET cases (Ref. 151). In addition, motor impairments including gait and balance abnormalities and continuous tremor were reported in GABA transporter subtype 1 gene (*Gat1*) knock-out mice (Ref. 152). However, no ET risk factor had been found in GABA transporter or receptor genes (Ref. 153).

Mutant rats with both the tremor (*tm*) mutation and the hyperpolarisation-activated cyclic nucleotide-gated 1 channel (*Hcn1*) mutation showed spontaneous tremors resembling ET, whereas rats carrying mutant *tm* or *Hcn1* alone presented no tremor, indicating ET may be a digenic inherited disease. Blocking HCN1 channels resulted in kinetic tremor in *tm* mutant rats, confirming the important role of *Hcn1* (Ref. 154). HCN1, a member of the HCN channel family expressed in heart and the nervous system (Ref. 155), can be activated by membrane hyperpolarisation, indicating a role in transportation of sodium and potassium ions (Ref. 154). The mutant HCN1 leads to restraint of hyperpolarisation-activated currents, suggesting a loss-of-function mechanism (Ref. 154). Several mutations in the sodium voltage-gated channel alpha subunit 8 gene (*Scn8a*) were found to result in congenital postural and kinetic tremor in mice of the extremities, as well as ataxia and dystonia, but after *SCN8A* screening of 95 Caucasian patients with familial ET, no causal mutation had been detected (Refs 156, 157).

The deficiency of a mouse PC gene, carbonic anhydrase 8 (*Car8*), was found to cause an ET-like tremor. The tremor mimics the ET condition of human in oscillation frequency, age-related progression and alcohol responsiveness (Refs 158, 159). Mutations in human carbonic anhydrase 8 gene (*CA8*), a homologue of *Car8*, was reported to result in tremor in addition to ataxia (Refs 158, 160), and the specific mechanisms need further studies.

Therapy

Therapy of ET is still symptomatic (Ref. 161), but the goal of current research is to find a pathogenesis-targeted treatment in the future. Therapy of ET can be roughly grouped into categories of pharmacologic, surgical and other nonpharmacologic or non-surgical treatment approaches (Ref. 1). Pharmacologic therapy, including four first-line drugs, such as propranolol, primidone, gabapentin and topiramate, is considered when tremor impacts daily living or psychological health (Refs 8, 162). Surgical therapy, such as thalamic deep brain stimulation or focused ultrasound thalamotomy, is reserved for drug-intolerant or drug-resistant patients with troublesome or disabling ET (Refs 163–165).

Future strategy

Genetic testing for ET has not reached mainstream clinical practice though several variants have been found in patients and families with ET. The plausible reasons include inconsistent definition of ET, ET misdiagnosis, age-related occurrence, complex genetic basis, incomplete penetrance, epigenetic modification, environmental disturbance and other factors, which may make it difficult to identify specific ET-related genes by current strategies (Ref. 166). ET is likely a syndrome with different subtypes and aetiologies. Observation of four disease-associated channel gene mutations (*SCN4A* p.G1537S, *SCN11A* p.R225C, *KSCN2*

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p.D379E and *CACNA1G* variants) in ET families, as well as mutant *Hcn1*, and *Scn8a* tremor animal models, indicates that different channel abnormalities may be responsible for subtypes of ET (Refs 12, 13, 72, 154, 156).

ET genetic studies may provide insights into the pathogenesis of the common disorder, improve diagnosis and eventually lead to more specific pathogenesis-targeted therapies. Analyses based on large sample size, diversified populations, CNV examination, modern omics sequencing techniques and cellular/system-level studies should be performed to investigate potential pathogenic and pathophysiological mechanisms of ET (Refs 2, 167).

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