

## REVIEW ARTICLE

## Genetics of essential tremor

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**Essential tremor (ET), the cause of which remains poorly understood, is one of the most common neurological disorders. While environmental agents have been proposed to play a role, genetic factors are believed to contribute to its onset. Thus far, three gene loci (*ETMI* on 3q13, *ETM2* on 2p24.1 and a locus on 6p23) have been identified in patients and families with the disorder. In addition, a Ser9Gly variant in the dopamine D<sub>3</sub> receptor gene on 3q13 has been suggested to be a risk factor. Moreover, genetically deficient animal models express a phenotype that overlaps with some clinical characteristics of the human form of the illness. Further analyses of these genetic abnormalities may lead to the identification of causative mutations and a better understanding of the molecular mechanisms in this common movement disorder.**

**Keywords:** essential tremor; genetics; dopamine D<sub>3</sub> receptor gene; variant; autosomal dominant; non-Mendelian inheritance

**Abbreviations:** ADCA = autosomal dominant cerebellar ataxia; AIS = androgen insensitivity syndrome; AR = androgen receptor gene; CAP2 = adenylate cyclase-associated protein 2 gene; CMT = Charcot–Marie–Tooth; CMTX = X-linked Charcot–Marie–Tooth; CYP2D6 = cytochrome P450IID6; *C6orf79* = chromosome 6 open reading frame 79 gene; DRD3 = dopamine D<sub>3</sub> receptor gene; DTNBP1 = dystrobrevin binding protein 1 gene; ERK1, 2 = extracellular signal-regulated kinase 1, 2; ET = essential tremor; *FMRI* = fragile X mental retardation 1 gene; FXTAS = fragile X-associated tremor/ataxia syndrome; *Gabra1* = gamma-aminobutyric acid A receptor  $\alpha$ 1; *GAT1* = GABA transporter subtype 1; *GFOD1* = glucose–fructose oxidoreductase domain containing protein 1 gene; *GMPT* = guanosine monophosphate reductase gene; HMSN = hereditary motor and sensory neuropathy; *HSIBP3* = HSI-binding protein 3 gene; *JARID2* = Jumonji AT rich interactive domain 2 gene; JNK = c-Jun NH<sub>2</sub>-terminal kinase; LD = linkage disequilibrium; *LRRK2* = leucine-rich repeat kinase 2 gene; MAPK = mitogen-associated protein kinase; MCR = minimal critical region; *MTHFR* = methylenetetrahydrofolate reductase gene; *MYLIP* = myosin regulatory light chain interacting protein gene; NACP = alpha-synuclein gene; *NHLRC1* = Nhl repeat-containing gene 1; *NOL7* = nucleolar protein 7 gene; *PHACTRI* = phosphatase and actin regulator 1 gene; *PMP2* = peripheral myelin protein-22 gene; *RANBP9* = RAN binding protein 9 gene; SAPK = stress-activated protein kinase; *SCA1, 12* = spinocerebellar ataxia gene, type 1, type 12; *SIRT5* = silent mating-type information regulation-2 homologue 5 gene; *SMAX1* = X-linked spinal and bulbar muscular atrophy, type 1; *TBCID7* = TBC1 domain family, member 7 gene

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## Clinical features and epidemiology

Essential tremor (ET), one of the most common neurological disorders, is characterized by postural tremor, which worsens with movement (Jankovic, 2002; Thanvi *et al.*, 2006). While action tremor is the clinical hallmark of this illness, it can also be found in a variety of disorders. For the purposes of this review, we define ET according to the clinical criteria proposed in the Consensus Statement on Tremor by the Movement Disorder Society (Deuschl *et al.*, 1998). A growing body of evidence suggests that this

disorder is not monosymptomatic but heterogeneous, as it is associated in some cases with parkinsonism, myoclonus, dystonia, cerebellar dysfunction and other motor and sensory (e.g. hearing impairment) abnormalities (Jankovic, 2002; Ondo *et al.*, 2003). Several studies have demonstrated that non-motor features (mild cognitive deficits and personality changes) may occur in patients with ET (Gasparini *et al.*, 2001; Lombardi *et al.*, 2001; Vermilion *et al.*, 2001; Lacritz *et al.*, 2002; Troster *et al.*, 2002;

Chatterjee *et al.*, 2004; Louis, 2005). In two recent case-control studies, patients performed more poorly on formal neuropsychological testing than control subjects without tremor. A complaint of forgetfulness and higher frequency of dementia was also marginally more common in patients with late-onset ET (Benito-Leon *et al.*, 2006a, b). The occasional coexistence of this disorder and other neurological diseases including Parkinson's disease, and dystonia in the same individual or the same family presents a diagnostic challenge (Geraghty *et al.*, 1985; Jankovic, 2000; Jankovic *et al.*, 2004; Shahed and Jankovic, 2006). Several studies have shown that a subset of ET patients may be predisposed to developing Parkinson's disease. This association is supported by the following evidence: (1) in some Parkinson's disease patients, a long-standing postural tremor in the hands may precede the onset of parkinsonian features by several years or decades; (2) functional neuroimaging suggests that some ET patients have dopaminergic deficit (Schwartz *et al.*, 2004) and (3) both ET and Parkinson's disease phenotypes have been described in some families and autopsy studies have demonstrated Lewy body pathology in brains of ET patients (Louis *et al.*, 2006; Shahed and Jankovic, 2006).

Estimates of the crude prevalence of ET range widely from 0.008 to 22%, and factors that contribute to the broad range include differences in study design that influence validity and differences in characteristics of study populations that influence comparability of studies. Louis *et al.* evaluated that the prevalence of ET worldwide ranges probably from 0.41 to 3.92% by extraction data from 5 of 19 studies with the conditions that each (i) provided diagnostic criteria for ET, (ii) defined ET as an action tremor and (iii) used community-based rather than service-based designs (Louis *et al.*, 1998; Benito-Leon *et al.*, 2005). There are no validated diagnostic tests for ET, but several clinical criteria have been proposed, including those by the Tremor Investigation Group (TRIG), National Institutes of Health Essential Tremor Consortium and Consensus Statement on Tremor by the Movement Disorder Society (Deuschl *et al.*, 1998; Jankovic, 2002). Lack of consensus on the diagnostic criteria for ET is an impediment to accessing accurate prevalence data.

Despite these limitations in defining the full spectrum of ET, typically it is not difficult to diagnose. Its prevalence increases in the elderly and may be as high as 14% in people over 65 years (Moghal *et al.*, 1994). Rare cases have been reported in newborns and infants, but childhood-onset ET is not unusual (Jankovic *et al.*, 2004), and ~5% of new ET cases arise during childhood (Louis *et al.*, 2005). Although prevalence among adults is similar in men and women (Louis *et al.*, 1998), the odds of developing the disorder are 3-fold higher in boys than girls. Head tremor is more prevalent in female than in male adults with ET (Jankovic *et al.*, 2004; Louis *et al.*, 2005). Mortality rates are not increased (Rajput *et al.*, 1984, 2004; Jankovic *et al.*,

1995), but the tremor may be quite troublesome and in some medically refractory cases surgical treatment (e.g. deep brain stimulation) may be necessary (Pahwa *et al.*, 2006).

## Genetics of ET

Twin and family studies have provided evidence for a genetic basis for ET in many but not all cases (Busenbark *et al.*, 1996; Tan *et al.*, 2000; Jankovic and Noebels, 2005). Linkage mapping efforts have found at least three loci for familial ET (*EMT1*, *EMT2* and a locus on 6p23) (Shatunov *et al.*, 2006), and a susceptibility variant (Ser9Gly) in the dopamine D<sub>3</sub> receptor gene (*DRD3*) has been identified by association analysis (Jeanneteau *et al.*, 2006; Lucotte *et al.*, 2006). Here we review the genetic aspects of ET, focusing on recent discoveries and how these findings may open a window into a better understanding of disease pathogenesis.

There is a wide range of familial history reported in ET patients, ranging from 17 to 100%, according to various studies (Busenbark *et al.*, 1996), but most studies indicate that it is a familial disorder in 50–70% of patients, and the frequency of family history is inversely proportional to the age at onset (Sullivan *et al.*, 2004; Louis and Ottman, 2006). For family studies, historical information on reportedly unaffected relatives is of limited use given the low sensitivity of family history; the neurological examination remains the only valid means of ascertaining cases of ET among relatives (Louis *et al.*, 1999, 2001). While familial cases are less frequent in community-derived populations, they constitute a majority in those referred for medical attention (Louis *et al.*, 2001). The occurrence of non-familial or 'sporadic' ET, phenomenologically identical to the familial version, is well-recognized and possible 'genetic causes' of sporadic ET include reduced penetrance of autosomal dominant mutations, new mutations, non-Mendelian/multifactorial inheritance and phenocopies. The genetics of ET is not well understood and twin studies provide a powerful tool to study it. Pairwise concordance in monozygotic twins was ~2 times that in dizygotic twins (0.60 monozygotic, 0.27 dizygotic), indicating that genetic and non-genetic factors contribute to pathogenesis (Tanner *et al.*, 2001). In one community-based study the relative risk in first-degree relatives of subjects with ET was only 4.7%, much lower than the 50% expected assuming autosomal dominant inheritance with complete penetrance (Louis, 2001). This rate is also lower than would be expected for autosomal recessive inheritance (25%) and may suggest that ET is an autosomal dominant gene with very low penetrance, or not inherited as a single gene disorder but rather behaves as a complex disorder requiring interactions of environmental and genetic factors. Alternative explanations include a polygenic or mitochondrial origin (Louis, 2001), and even autosomal recessive and X-linked patterns of inheritance can not be excluded

(Baughman *et al.*, 1973). Furthermore, recently Ma *et al.* (2006) found a non-Mendelian preferential transmission of the affected allele in several families with multiple affected members and apparent autosomal dominant inheritance. Genetic deficiency or non-genetic factors may exert sole or synthetic roles in the development of ET in independent patients or families.

## Genetic loci of ET

### Cytogenetic abnormality

ET-like tremor seems to be common and a clinically significant component of the male supernumerary X syndromes and supernumerary Y syndromes (Baughman *et al.*, 1973). A 14-year-old boy with 48, XYY karyotype was reported to present with postural tremor and a slight retardation of psychomotor development. In contrast to other cases with 48, XYY syndrome, in this pubertal patient the testicles were of normal size, he had a small stature, and showed no behavioural disturbances (Donati *et al.*, 1992). These findings suggest that dosage alteration of genes on sex chromosomes may be responsible for an ET phenotype.

### Molecular studies

At least three disease loci of ET have been identified by molecular genetic analysis (Table 1).

#### *ETM1 (3q13, OMIM 190300)*

In 1997, Gulcher *et al.* (1997) mapped a familial ET gene to chromosome 3q13 (*FET1*; *ETM1*) by a genome-wide scan in 16 Icelandic families with 75 individuals affected by definite (pure) tremor using TRIG criteria (Findley and Koller, 1995), in whom *FET1* was apparently inherited as a dominant trait. The *ETM1* locus spans ~10 cM region around the marker D3S1267. More recently, a Ser9Gly variant in the *DRD3* gene, located in the *ETM1* locus, was found associated with risk and age at onset of ET (Jeanneteau *et al.*, 2006). The *DRD3* gene encodes the dopamine D3 receptor, a member of the D2 family of dopamine receptors. D3 receptors may be involved in the regulation of locomotion as DRD3 protein is expressed in the Purkinje cells of the rat cerebellum, which has been implicated in the pathogenesis of ET (Jeanneteau *et al.*, 2006). DRD3 has been also reported to mediate ERK activation in HEK-293 cells (Beom *et al.*, 2004). In HEK293 transfected cells, the functional Gly9 variant increased dopamine affinity 4–5 times. Furthermore, the Gly9 variant was associated with increased dopamine-mediated cyclic AMP response and the mitogen-associated protein kinase (MAPK) signal was prolonged, as compared to the Ser9 variant. In mammalian cells, at least three groups of mitogen-activated protein kinases (MAPKs) have been identified: the extracellular signal-regulated kinases (ERK1 and 2, which increase the kinase activity of ERK1/2 to regulate many cellular events such as differentiation,

proliferation, cellular excitability and acute hormonal responses), the p38 protein kinases and the c-Jun NH2-terminal kinases (JNKs; also referred to as stress-activated protein kinases or SAPKs) (McDonald *et al.*, 2000). It is of interest that the leucine-rich repeat kinase 2 gene (*LRRK2*) G2019S and I2020T mutations, which have been associated with autosomal dominant Parkinson's disease, have now been shown to increase the catalytic activity of the MAPKKK domain, a part of the *LRRK2* protein (Deng *et al.*, 2005b, 2006a, b), and *LRRK2* mutations eventually also lead to the activation of downstream MAPK kinases. Abnormalities in the JNK signalling pathway may also account for dopaminergic cell degeneration in patients with *LRRK2* mutation. An increase in MAPK activity (such as induced by the *DRD3* Gly9 variant or by some *LRRK2* mutations) may be a common mechanism partly responsible for the pathogenic events leading to ET and Parkinson's disease, which may explain the observed overlap in phenotype or coexistence of ET and Parkinson's disease in some cases (Shahed and Jankovic, 2006). It is not clear whether the Ser9Gly variant has been shown to cosegregate with the disease in the original 16 Icelandic families linked to *ETM1* (Gulcher *et al.*, 1997).

#### *ETM2 (2p24.1, OMIM 602134)*

In 1997, Higgins *et al.* (1997) mapped the *ETM2* gene to a 15-cM candidate interval on chromosome 2p22–p25 by linkage analysis in a large American family of Czech descent with dominantly inherited 'pure' ET. The disease gene was located to a 9.1-cM interval between the *D2S224* and *D2S405* loci by analysing three additional, unrelated, American families with ET; the affected individuals in the four families shared the same haplotype (Higgins *et al.*, 1998). They further found an ancestral haplotype on chromosome 2p24.1 that segregated with the ET disease phenotype in 29% American familial ET individuals ( $N=45$ ) (Higgins *et al.*, 2003). Kim *et al.* (2005) reported an association analysis of three short tandem repeat (STRs) loci in 30 sporadic ET (23 classic ET and 7 non-classic ET) patients and 30 controls. Furthermore, eight specific sequence variants were observed in classic ET, but not in non-classic ET patients or healthy controls, supporting the linkage of ET to the *ETM2* locus. An association between ET and an A265G substitution in the HS1-binding protein 3 gene (*HS1BP3*, OMIM 609359) was reported by analysis of two genes and seven transcripts within a minimal critical region (MCR) of 464 kb (Higgins *et al.*, 2005, 2006). However, four recombination events were reported in a region <1 cM (*D2S2150* to *etm1234*) in the large family (Higgins *et al.*, 2005), and the MCR has been challenged (Deng *et al.*, 2005a). Furthermore, the association with the *HS1BP3* gene was neither confirmed by our extended study nor by other investigators (Deng *et al.*, 2005a; Shatunov *et al.*, 2005). Based on our review of previous studies (Higgins *et al.*, 1997, 1998, 2003, 2004), we

**Table 1** Molecular genetic analysis of three candidate loci of ET

Chromosome position	Author	Sample size	Inheritance model	Ethnic or geography distribution	Locus-disease relationship	Candidate gene analysis	
3q13 ( <i>ETM1</i> )	Gulcher <i>et al.</i> (1997)	16 families	AD	Iceland	Related	Not	
	Kovach <i>et al.</i> (2001)	1 family	AD	Midwestern America	Not related	Not	
	Illarioshkin <i>et al.</i> (2002)	4 families	AD	Tajik	Related	Not done	
	Lucotte <i>et al.</i> (2006)	30 unrelated French ET	AD or polygenic	French	Related	<i>DRD3</i> -Ser9gly variant (risk)	
	Jeanneteau <i>et al.</i> (2006)	276 patients, 184 controls	AD or polygenic	Caucasian from America	Related	<i>DRD3</i> -Ser9gly variant (risk)	
	Ma <i>et al.</i> (2006)	4 families	AD and polygenic?	America	Not related	<i>DRD3</i> -Ser9gly variant (exclude causative)	
2p24.1 ( <i>ETM2</i> )	Higgins <i>et al.</i> (1997)	1 family	AD	American kindred of Czech ancestry	Related	Not	
	Higgins <i>et al.</i> (1998)	3 families	AD	America	Related	Not	
	Higgins <i>et al.</i> (2004)	52 ET patients, 49 controls	Not reported	Singapore	Related	Not	
	Kim <i>et al.</i> (2005)	30 sporadic ET patients and 30 controls	Not reported	Korea	Related	Not	
	Higgins <i>et al.</i> (2005)	21 families, 150 controls	AD	America	Related	<i>HSIBP3</i> (A265G variant) (causative)	
	Higgins <i>et al.</i> (2006)	73 familial ET, 304 controls	AD	America	Not reported	<i>HSIBP3</i> (A265G variant) (causative)	
	Deng <i>et al.</i> (2005a)	222 familial ET, 132 controls	Not reported	North America	Not reported	<i>HSIBP3</i> (A265G variant) (exclude causative or risk)	
			1 family	AD	North America	Not related	<i>HSIBP3</i> (A265G variant) (exclude causative or risk)
		Shatunov <i>et al.</i> (2005)	7 families	Not reported	America	Not reported	<i>HSIBP3</i> (A265G variant) (exclude causative or risk)
		Kovach <i>et al.</i> (2001)	1 family	AD	Midwestern of America	Not related	Not
6p23 ( <i>ETM3?</i> )	Ma <i>et al.</i> (2006)	4 families	AD and polygenic?	America	Not related	Not	
	Shatunov <i>et al.</i> (2006)	1 family	AD	North American	Related	<i>PHACTR1</i> ; <i>TBCID7</i> ; <i>GFOD1</i> ; <i>SIRT5</i> ; <i>NOL7</i> ; <i>RANBP9</i> ; <i>LOC441130</i> ; <i>C6orf79</i> ; <i>JARID2</i> ; <i>DTNBPI</i> ; <i>MYLIP</i> ; <i>GMPR</i> ; <i>SCAI</i> ; <i>CAP2</i> ; <i>NHLRC1</i> (no mutation)	

AD: autosomal dominant.

believe that the *ETM2* locus may span ~9.1 cM region, between the *D2S224* and *D2S405* loci, and the MCR should be re-evaluated.

Genetic heterogeneity in ET has been suggested by studies in several families in which the known loci have been excluded. Kovach *et al.* (2001) described a 38-member, 6-generation Midwestern family with ET that did not map to either the *ETM1* or the *ETM2* loci. In another study, four pedigrees with ET were linked to *ETM1*, but in one informative pedigree both *ETM1* and *ETM2* were excluded (Illarioshkin *et al.*, 2002). Ma *et al.* (2006) also excluded *ETM1* and *ETM2* loci in four pedigrees. Recently, genome-wide non-parametric and parametric linkage analysis were conducted in seven multigenerational North American families totalling 65 patients. In two families the third ET susceptibility locus was revealed on chromosome 6p23 with maximal non-parametric linkage multipoint score 3.281 ( $P=0.0005$ ) and 2.125 ( $P=0.0075$ ), respectively. Linkage to *ETM1* and *ETM2* was not evident in any of these families. Fifteen genes were selected as plausible candidates and none of them was found to bear pathogenic mutations (Shatunov *et al.*, 2006).

### Candidate gene analysis for ET

Many studies have documented an overlap between the ET phenotype and other neurological diseases including Parkinson's disease, dystonia, myoclonus, hereditary peripheral neuropathy and other neurological disorders (Jankovic, 2002; Shahed and Jankovic, 2006). Therefore, analyses of gene abnormalities known to cause the associated neurological disorders may provide insight into the genetics of ET.

### Analysis of Parkinson's disease-associated genes

ET has been hypothesized to be a risk factor for the development of Parkinson's disease and some patients with Parkinson's disease report a long-standing history of bilateral upper extremity postural tremor long before the onset of parkinsonian features, such as rest tremor, bradykinesia and rigidity. While patients with Parkinson's disease may also have postural tremor, the Parkinson's disease-related postural tremor often occurs after a long latency, lasting ~10–20 s (up to a minute or even longer), whereas there is usually no delay in the onset of postural tremor caused by ET when the arms assume horizontal position (Jankovic *et al.*, 1999). Mutations in the *parkin* gene is the most common cause for early onset Parkinson disease (EOPD), which is responsible for 49% of familial EOPD and 18% of sporadic EOPD (Lucking *et al.*, 2000). No mutation in the *parkin* gene was identified in 110 unrelated Italian ET patients (Pigullo *et al.*, 2004). Several studies observed an association of alpha-synuclein haplotypes including *NACP-Rep1* (A 263 bp allele in the alpha-synuclein promoter region) with Parkinson's disease, but other studies failed to confirm this association

and an inverse association between the alleged risk allele and Parkinson's disease was reported in a Japanese population (Kruger *et al.*, 1999; Farrer *et al.*, 2001; Mizuta *et al.*, 2002; Holzmann *et al.*, 2003; Spadafora *et al.*, 2003; Pals *et al.*, 2004; Hadjigeorgiou *et al.*, 2006). Recently, *NACP-Rep1* was found associated with an increased risk of Parkinson's disease by analysis of 2692 cases and 2652 controls (Maraganore *et al.*, 2006). Tan and colleagues (2000) confirmed that the 263 bp variant was significantly more frequent (OR = 6.42) in American ET patients (46 cases) compared with healthy controls (100 cases). Pigullo *et al.* (2003), however, repeated the association study on 106 Italian patients and 90 controls and failed to identify all 13 alpha-synuclein-specific haplotypes as susceptibility factors for ET. The contrasting results and lack of replication for the association of such variant with ET could depend on the very small number of patients and controls in both studies, and therefore these results are not conclusive and larger studies would be necessary to address this issue. Of interest was that one female Parkinson's disease patient harboring *LRRK2* IVS33 + 6T → A variant presented initially with a typical ET phenotype and her symptoms responded well to propranolol (Skipper *et al.*, 2005). Investigation of this variant in ET or Parkinson's disease with ET patients may provide some insights into the genetics of ET. We found none of *LRRK2* G2019S, I2012T and I2020T mutations in 272 ET patients, suggesting that they are rare causes of Caucasian ET (Deng *et al.*, 2006a) and other mutations in the *LRRK2* gene may be investigated in ET patients. Although an association between cytochrome P450IID6 (*CYP2D6*) variant and Parkinson's disease has been reported, the study of Agundez *et al.* (Agundez *et al.*, 1997) indicates that variants in the *CYP2D6* gene do not seem to be a major factor in determining susceptibility to ET.

### Analysis of dystonia-associated gene

Although the frequent coexistence of ET and dystonia has been reported in individual families (Jankovic *et al.*, 1997), and autosomal dominant idiopathic torsion dystonia shares some phenotypic features with ET, such as postural tremor in body parts not affected by dystonia (Jankovic and Mejia, 2005), tight linkage to the *DYT1* locus on chromosome 9q32–34 was excluded in two independent studies by analysis of 13 families with ET (Conway *et al.*, 1993; Durr *et al.*, 1993). In 2002, Illarioshkin *et al.* (2002) reported that mutation analysis of the *DYT1* gene did not reveal the typical GAG deletion in ET patients.

### Analysis of other genes

Postural tremor similar to that seen in ET has been reported in patients with X-linked spinal and bulbar muscular atrophy, type 1 (SMAX1, OMIM 313200), also called Kennedy disease, associated with androgen insensitivity syndrome (AIS; OMIM 300068), which is caused by a mutation characterized by expansion of CAG repeats in the androgen receptor gene (*AR*, OMIM 313700) on the

X chromosome (La Spada *et al.*, 1991; Jakubiczka *et al.*, 1997; Sperfeld *et al.*, 2002). A man diagnosed with ET, but found to have increased CAG repeats in the AR gene consistent with Kennedy disease, has been reported (Kaneko *et al.*, 1993). Although he had postural tremor of his fingers, the diagnosis of Kennedy syndrome is supported by the presence of fasciculations in facial muscles and long-duration, high-amplitude polyphasic motor units, with decreased recruitment on voluntary contraction in limb muscles along with evidence of motor neuropathy by electromyographic studies.

Spinocerebellar ataxia type 12 (SCA-12) is a slowly progressive autosomal dominant cerebellar ataxia (ADCA) that differs from other SCAs because it typically begins with tremor of head and arms, often diagnosed as ET. Nicoletti *et al.* (2002) investigated 30 patients with familial ET from southern Italy and found none with the SCA-12 mutation.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a progressive adult-onset tremor/ataxia syndrome caused by premutations in the fragile X mental retardation 1 gene (*FMR1*). Major features of the syndrome include intention tremor, gait ataxia and parkinsonism in men over 50 years of age (Leehey *et al.*, 2003; Jacquemont *et al.*, 2004), and studies of ours and others showed permutation of *FMR1* probably plays little or no role in the pathogenesis of ET in Caucasian and Asian patients (Deng *et al.*, 2004; Garcia *et al.*, 2004; Tan *et al.*, 2004).

C677T variant of methylenetetrahydrofolate reductase gene (*MTHFR*) has been associated with neurodegenerative disorders including Parkinson's disease and Alzheimer's dementia (Chapman *et al.*, 1998; Pollak *et al.*, 2000; Yasui *et al.*, 2000; Nakaso *et al.*, 2003). Sazci *et al.* (2004) reported that the C677C/A1298A compound genotype provided protection for ET, while the *MTHFR* 677T, 1298C alleles and *MTHFR* T677T genotype and T677T/A1298A, and C677C/C1298C compound genotypes are genetic risk factors for ET in Turkey. The correlations must be confirmed in different ethnic populations and by functional studies.

### Potential loci and genes of ET

ET-like tremor was found in patients with hereditary neuropathy including hereditary motor and sensory neuropathy (HMSN; Charcot–Marie–Tooth, CMT) and the Roussy–Levy syndrome (RLS, OMIM 180800), etc (Cardoso *et al.*, 1993; Auer-Grumbach *et al.*, 1998). ET-like tremor was observed in an X-linked CMT (CMTX) patient who carried 13-bp deletion in the connexin-32 gene (Ryan *et al.*, 2005). Although mistimed peripheral inputs due to neuropathy may cause tremor irrespective of an intact central processor (Bain *et al.*, 1996), some features of ET can be part of the phenotypic spectrum of some peripheral neuropathies and therefore genes causative of these neuropathies including *connexin-32* and the peripheral myelin protein-22 gene (*PMP22*) could be regarded as potential candidates for ET.

### Animal models with genetic deficiency

Animal models are important because they provide insights into the pathophysiology of human disease and may be useful in the development of novel drugs. Gamma-aminobutyric acid<sub>A</sub> receptor  $\alpha 1$  (*Gabra1*<sup>-/-</sup>) mice were reported to exhibit postural and kinetic, alcohol-responsive tremor that is characteristic of ET disease (Chiu *et al.*, 2005), but no pathogenic mutations in the *GABRA1* gene have been found by testing 76 patients with familial ET (Deng *et al.*, 2006c). Mouse GABA transporter subtype 1 (*GAT1*) knock out mice exhibit gait abnormality, constant 25–32 Hz tremor, which is aggravated by flunitrazepam, reduced rotarod performance and reduced locomotor activity in the home cage. As disturbed GABA-ergic transmission may play a role in the pathogenesis of ET, suggested by low CSF GABA concentrations in ET patients compared to controls (Mally *et al.*, 1996), and the tremor can be suppressed by medications that work by GABA-ergic mechanisms, including alcohol and benzodiazepines, human *GAT1* gene may be a possible candidate gene for ET.

### Current problems in ET genetics and prospects for strategy

Although the preponderance of data supports the view that ET susceptibility is inherited in an autosomal dominant pattern, other models should be considered. Further understanding of the extent of familial aggregation, extent of genetic heterogeneity and mode of inheritance is essential for clinical counselling and for further research aimed at localizing and identifying susceptibility genes.

The various terms used in the study of genetics of various disorders, including ET, need to be clearly defined. Thus, the term 'sequence variation' is used to prevent confusion with the terms 'mutation' and 'polymorphism'. The term 'mutation' should be reserved for a sequence variation that is disease-causing or apparently disease-associated, although it can also be used to describe any sequence change. However, a polymorphism largely means a 'non-disease-causing change with a frequency of 1% or higher in the population' (den Dunnen and Antonarakis, 2001). We suggest that the term 'variant' is used when it is not certain whether change in nucleotide or the amino acid is a risk or a cause for disease, or a confirmed risk factor for disease. This term encompasses 'polymorphism' and 'mutation'.

The *DRD3* Ser9Gly variant, a potential risk factor for schizophrenia, obsessive–compulsive personality disorder, tardive dyskinesia and other disorders (de Leon *et al.*, 2005; Keri *et al.*, 2005; Light *et al.*, 2006), was also recently found associated with increased risk for ET. This common Gly9 variant is probably a risk allele and may become pathogenic when internal or external environmental stress is present. Identification of variants that are associated with ET, especially if they lead to an abnormal gene expression or a change of amino acid sequence may exert

a combined or synergistic effect on susceptibility to disease (Sivagnanasundaram *et al.*, 2000).

In future genetic studies it may be useful to subdivide ET into several subtypes based on whether it is present as a monosymptomatic disorder or whether it coexists with other neurological diseases, age at onset and other variables (Benito-Leon *et al.*, 2006). For Mendelian inheritance ET pedigrees, regular mapping–cloning strategy including parametric linkage analysis and candidate gene screening may be employed, while non-Mendelian inheritance pedigrees or sporadic patients need to validate a gene–disease relationship through comparative analysis of linkage disequilibrium (LD) and disease-association patterns (Jonsson *et al.*, 2003; Farrer, 2006). Although comparison of genotypes between ET patients and controls among different ethnicities may lead to the identification of disease-specific and ethnicity-specific genome variations, most insight might be gained by studying the functions of genes. Identification of the defective gene or risk allele will enable a better understanding and classification of ET, as well as genetic counselling and therapy of this disorder.

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