

# 'Essential Tremor' or 'the Essential Tremors': Is This One Disease or a Family of Diseases?

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## Key Words

Essential tremor · Disease · Classification · Pathology · Genetics · Clinical features · Heterogeneity · Neurodegeneration

## Abstract

There is accumulating evidence that the entity referred to as 'essential tremor' (ET) is not a single disease. It may be a family of diseases better referred to as 'the ETs'. This review will summarize the following evidence: (1) the presence of etiological heterogeneity; (2) the heterogeneity of findings in postmortem studies, thus suggesting several diseases; (3) the recent discussion that age of onset may be an important marker of disease heterogeneity; (4) the clinical expansion of the concept of ET in recent years to include a broader range of tremor phenomenology, other motor features (gait ataxia), other involuntary movements (dystonia), and nonmotor features (cognitive problems, psychiatric problems), some of which could be primary; (5) the heterogeneity of pharmacological response profiles and clinical progression, and (6) the association of ET with Parkinson's disease, Alzheimer's disease, and possibly progressive supranuclear palsy, with the possibility that some ET patients are more predisposed to develop one of these.

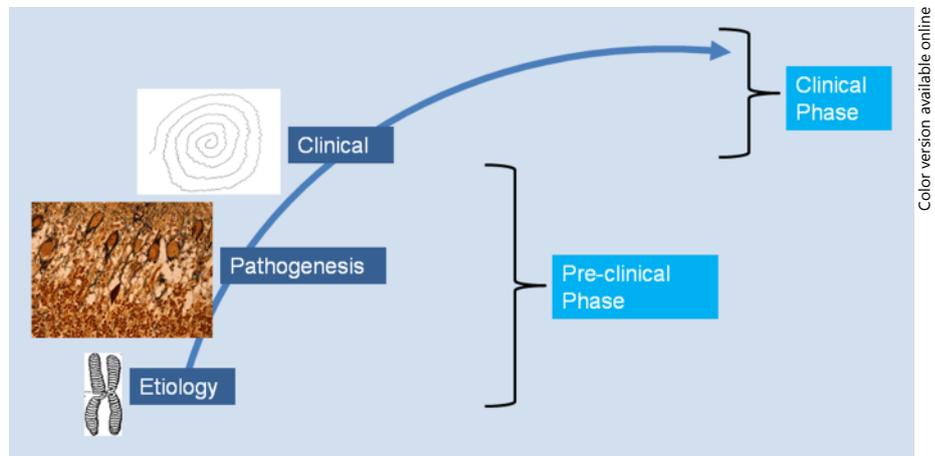
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## Introduction

Although tremor and, more specifically, essential tremor (ET) have long been known to humans [1–3], knowledge of ET has grown markedly over the past decade [4]. Indeed, the familiar neurological condition long ago labeled 'ET' [1] is becoming more difficult to fully encapsulate. Current thinking about the fundamental nature of this diathesis is evolving. Indeed, it is quite likely that ET is a family of related diseases, unified by a common symptom/sign, namely, action tremor (i.e. tremor during voluntary movement). In this sense, the label 'the ETs' would be more appropriate. This review will summarize and discuss the relevant data.

## Methods

The author used PubMed (1966 to April 2013) to cross-search the terms 'tremor', 'essential tremor' and 'etiology', 'genes', 'familial', 'environmental', 'toxins', 'causes', 'epidemiology', 'clinical', 'phenotype', 'brain', 'cerebellum', 'Purkinje', 'Lewy body', 'degeneration', 'treatment', and 'medication' and reviewed all English language papers. The author supplemented this review with published peer-reviewed papers in his own files.



**Fig. 1.** The disease process in ET as an etiological-biological-clinical continuum.

## Results

### *Etiologic Heterogeneity in ET*

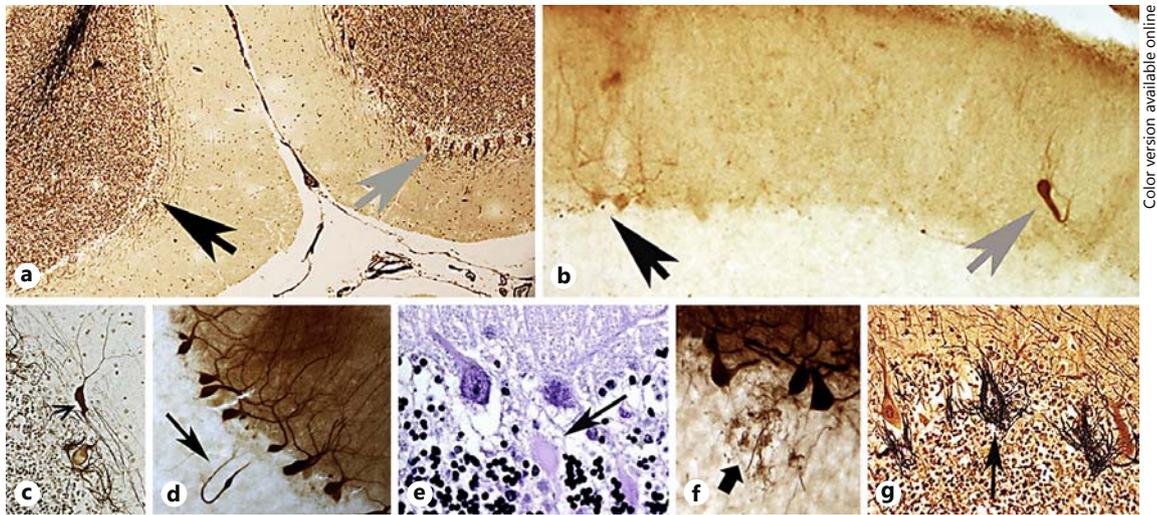
Disease etiology refers to the initial or primary cause of the disease, and it is comprised either of genetic or environmental factors; in some cases, both genetic and environmental factors may be operating alone or in combination (fig. 1) [5]. ET is a worldwide condition with a high prevalence [6–12]. The disorder also has a relatively restricted phenotype in the sense that the number of clinical features is relatively small. It is likely that there are many gene carriers and that carriers of different genes express an identical or nearly identical set of clinical features. Linkage studies have demonstrated at least three loci (2p22, 3q13, and 6p23) that are of possible significance in ET [13–15]. More recently, genome-wide association studies have identified a number of common variants that are associated with a modest elevation in risk of ET [16, 17]. Thus, with respect to ET, the presence of multiple genes (genetic heterogeneity) is accepted [18, 19]. Some of these genes are likely to be rare, as seems to be the case with the fused in sarcoma (FUS) gene [20–22], further suggesting that the eventual number of known identified genes might be sizable. If one takes the one gene-one disease approach [23], the presence of such genetic heterogeneity suggests that ET is not one disease; rather, ET would be a family of diseases. Leaving aside this one source of heterogeneity (i.e. genetic heterogeneity), one must also consider other sources of etiological heterogeneity. It is generally agreed upon that there are both familial and sporadic forms of ET [24], thereby more widely indicating the presence of etiological heterogeneity beyond the domain of genes. The cause(s) of these sporadic forms of ET are fully unknown, yet in association studies,

a wide array of neurotoxins has been investigated, and several of these, including harmane, lead, and ethanol, could play a role in disease etiology [25]. Studies are suggesting that some of the toxins are of greater importance in the familial than sporadic form of ET [26], suggesting the presence of either gene-environment interaction or a two-hit (increased genetic susceptibility followed by exposure to environmental factor) model of disease. It is unclear how these various genes and environmental factors operate in a single population and across different populations. Regardless, the presence of etiological heterogeneity strongly suggests the possibility of a multiplicity of disease entities rather than only one.

### *Heterogeneous Pathogenesis*

Disease pathogenesis, which follows etiology, refers to the cascade of molecular, cellular, and then tissue/organ-based changes that occur after the disease is set in motion. It follows etiology (fig. 1).

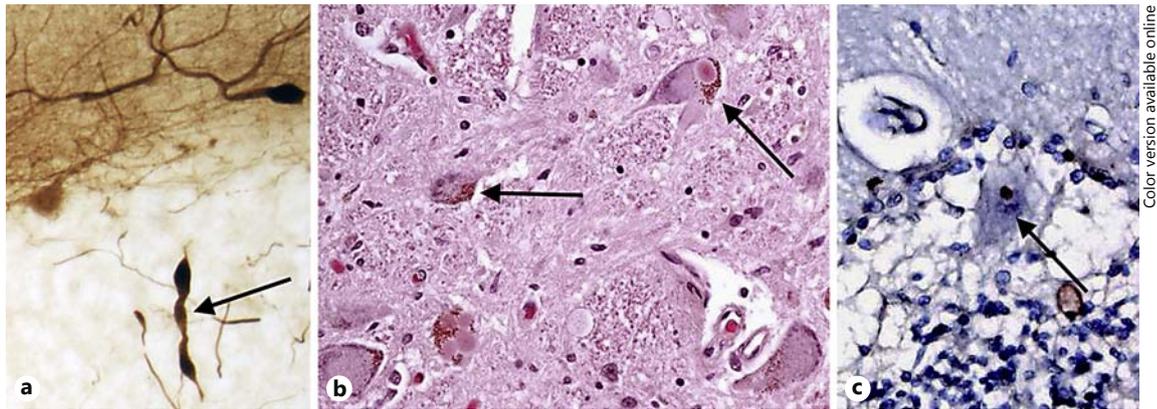
In various neurodegenerative diseases of aging, the presence of pathological heterogeneity has led investigators to question the unitary nature of the diathesis. Thus, although we refer to Alzheimer's disease (AD) as a single disease entity with a common neuropathological hallmark, there are clearly distinct patterns/distributions of these features [27]. Some have even indicated that we must conceptualize the ADs 'as a heterogeneous disorder or a family of Alzheimer diseases based on specific mechanism(s) rather than a single, neurodegenerative disorder dominated by beta-amyloid neuritic plaques and tau-based neuronal neurofibrillary change' [28]. The absence of Lewy bodies in some Parkinson's disease (PD) cases has also led investigators to raise the issue as to whether PD is one or more diseases [23]. As will be discussed below, in the setting of



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**Fig. 2.** A variety of structural microscopic changes have been described in the ET cerebellum on postmortem examination, and these seem to be centered on the Purkinje cell and surrounding neuronal populations (i.e. Basket cells). Cerebellar cortical sections in ET cases. **a** Relatively normal Purkinje cell layer (gray arrow on the right) near an area with segmental loss of Purkinje cells (black arrow on the left). Bielschowsky stain. **b** A heterotopic Purkinje cell (gray arrow) is adjacent to two normal Purkinje cells

(black arrow). Calbindin-stained section. **c** A swelling (arrow) of the Purkinje cell dendrite. Bielschowsky stain. **d** A torpedo, thickened axon, and recurrent axonal collateral (arrow). Calbindin stain. **e** Two torpedoes adjacent to their respective Purkinje cell soma. Luxol fast blue HE stain. **f** Sprouting of Purkinje cell axonal end processes in the upper granular layer. Calbindin stain. **g** Hypertrophic Basket cell processes and an empty basket (arrow). Bielschowsky stain.



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**Fig. 3.** Three different ET cases showing a heterogeneity of pathological findings in the ETs. **a** Representing cerebellar pathology, a Purkinje cell axon is shown with three torpedoes. Calbindin stain.

**b** Multiple Lewy bodies in the locus coeruleus. HE stain. **c** Ubiquitin-positive Purkinje cell intranuclear inclusion.

mounting evidence of pathological heterogeneity, a similar issue is now arising in ET as well.

ET is increasingly being viewed as a disease of the cerebellum and its connections [29–34]. A variety of changes have been described in the ET cerebellum on postmortem examination, and these seem to be centered on the Purkinje cell and surrounding neuronal populations (i.e. Basket cells) (fig. 2) [29]. These changes resemble to some

extent the types of changes seen in patients with disorders of cerebellar degeneration [35–37].

One feature that has been reported consistently across studies is the heterogeneity of pathological findings in ET [38–40]. Indeed, this had led earlier investigators to conclude that there was no consistent pattern of pathology [39], yet in reality, the heterogeneity does follow certain preliminary patterns (fig. 3). Thus, in those brain banks

that have carefully quantified a full range of pathological changes in the cerebellum (New York), the majority of ET cases have a clearly identifiable set of postmortem structural changes and have been referred to as ‘cerebellar ET’ (fig. 2) [38]. A smaller portion has brainstem Lewy bodies [41, 42], and an even smaller portion has intranuclear inclusions in the cerebellum and elsewhere [43, 44]. The number of ET brains that have come to postmortem is still small, and enlargement of the sample size is needed to better understand the basic patterns and make full sense of this emerging picture of pathological heterogeneity. It is even possible that ‘cerebellar ET’ itself might be comprised of several disorders, with each characterized by a slightly different signature of postmortem changes in the cerebellum.

An additional consideration is that there are differences across brain banks with respect to some findings, with one bank unable to detect Purkinje cell loss in ET, for example [34, 45]. Different findings across brain banks likely reflect differences in sampling, differences in case definition, and other important methodological issues like sample size [29, 38, 39, 41, 46]; it is also possible that these differences reflect true heterogeneity.

#### *Age of Onset Tremor: A Marker of Heterogeneity*

Although ET may arise at any age [47, 48], from infancy through advanced age, this does not mean that the incidence and prevalence of disease are randomly distributed with respect to age. The incidence of ET follows a blueprint, with a rising incidence during advanced aging [49, 50]. There has been some recent discussion that later-onset ET (age  $\geq 65$  years) should not be regarded as ET per se, but should be regarded as ‘senile tremor’ [51]. In spite of the notion that age of onset may be a disease feature of mechanistic interest, the particular choice of this cut point does not have much biological support. Furthermore, when other disorders (e.g. AD and PD) occur at or after the age of 65, one does not refer to them as ‘senile dementia’ or ‘senile parkinsonism’. The notion that ET must occur prior to the age of 65 is unfounded; indeed, it has been demonstrated in familial forms of the disorder that penetrance is not even complete by the age of 65 years [52]. The term ‘senile tremor’ is an arcane term that was used early in the last century, and it is not a particularly useful construct today. A more biologically meaningful age-related observation is that younger-onset ET cases are more likely to be familial and, presumably, genetic [53]. Hence, certain distinct classes of etiologies (i.e. genes rather than environmental factors) may influence the timing of disease on-

set and possibly the expression of disease. Thus, age of onset heterogeneity likely reflects etiological and biological heterogeneity.

#### *Clinical Features and Clinical Heterogeneity*

Some degree of action tremor is nearly universal among adults – physiological tremor and enhanced physiological tremor [54]. In addition, a wide range of tremor disorders has been described [55]. There is a tendency for clinicians to be ‘lumpers’, overapplying the diagnosis ‘ET’ to many of these conditions and treating ET as if it were formless [48, 56, 57]. Yet, far from being featureless and nondescript, the disease, ET, is characterized by specific and consistently described pattern(s) of tremor: (1) kinetic tremor is greater than postural tremor [58, 59]; (2) there is an involvement of specific joints in specific directions (e.g. wrist tremor is greater than metacarpal tremor, wrist flexion-extension tremor is greater than wrist rotation tremor) [60]; (3) intention tremor of the arms occurs in approximately 50% of cases [61, 62]; (4) rest tremor as a late feature occurs in up to 20% of cases [63]; (5) arm tremor precedes cranial tremor, of which there is a female preponderance [64, 65]; (6) there is a prevalence of neck greater than jaw greater than tongue/cheek/forehead tremor [66]; (7) there is a tendency for tremor severity to increase over time [67, 68], and (8) there is a co-occurrence of cerebellar features aside from intention tremor (e.g. gait ataxia) in many patients [69, 70]. Thus, in addition to these consistencies of pattern (i.e. a symptom complex), there is a general course/prognosis across patients.

With an increase in case-control studies over the past 5–10 years, which have supplemented older case series (i.e. cases without controls), there has been a growing appreciation that the clinical phenomenology that can accompany the base features of ET can be quite varied in nature and differentially expressed across patients (i.e. different phenotypes) [71]. First, there is an evolving awareness and acceptance of the presence of cerebellar features in some but not all patients [64, 72–78]. In an unknown proportion of patients, these are more marked. Their pathophysiological significance is not fully clear. Second, it is becoming clear that other involuntary movements (e.g. dystonia) may co-occur with ET in some individuals, especially in familial forms of ET [79, 80]. This raises the question as to whether mild torticollis and other features of dystonia may occur in longstanding/severe and/or familial forms of ET without the need to invoke a second or alternative diagnosis [79]. Third, nonmotor features (cognitive problems ranging from mild to severe [81–87] and psychiatric problems [88–92], some of which

could be primary [93, 94]) are increasingly being seen as a feature of some patients (e.g. those with older age of onset) [95]. Heterogeneity of clinical progression has also been pointed out [96–98]. Together, these data point to a general yet ill-defined sense that clinical heterogeneity is likely to be an expression of disease state (e.g. disease duration and severity at the time point of the clinical observation), but that it may also reflect diverse disease trait(s) (phenotype, pathomechanisms).

#### *Heterogeneity of Pharmacological Response Phenotype*

Nearly all of the treatments that have shown to be effective for ET, to date, involve the enhancement of a single and specific brain neurotransmitter system [i.e. the  $\gamma$  amino butyric acid (GABA)-ergic system]. This would include the barbiturates, primidone, benzodiazepines, gabapentin, and even various alcohols [99]. This indicates that there is a specific central target of underlying biological importance.  $\beta$ -Blockers probably likely act at a very distal (i.e. peripheral) site [99].

For a variety of clinical trials in ET, treatment graphs (before and after treatment) clearly show that a sizable portion (30–60%) of patients has little if any response to medication; the remaining subgroup of patients do show evidence of a response [100–103]. Some of this heterogeneity could be accounted for by differences in disease duration along with the probability that the underlying biological substrate advances over time (i.e. likely a reflection of disease ‘state’ rather than ‘trait’), leaving less room for clinical responsiveness [104], as occurs in PD [105] and AD [106, 107]. Some of these differences, though, could be ‘trait’ differences (i.e. separate diseases that are all lumped into and labeled as ‘ET’). Of interest is that there is less response heterogeneity with deep brain stimulation surgery, with the large majority of ET patients showing a sizable response to the intervention [108]. This is likely because the intervention is acting at the level of the thalamus, which is a more distal-final common nodal point for the receipt of diatheses-affected pathways that emerge from various more proximal points within the cerebellar system in ET.

#### *Do Different ‘ETs’ Lead to Different Outcomes?*

In case-control and cohort studies, ET has been linked with several other neurodegenerative conditions [109]. Though considered controversial [110], there are no other epidemiological data to the contrary [111]. Thus, there is a reported association of ET with PD [112–115], ET with AD [95, 116, 117], and ET with progressive supranuclear palsy [39, 118]. It will be important to identify the

subgroups of patients who are at increased risk for each of these entities. One would expect that these subgroups of prevalent ET cases might have basic pathophysiological features that distinguish them from those who are not at increased risk.

## **Discussion**

Debates over nosology and disease classification can become quite intense, yet they often serve to bring to the fore useful discussion points, and they can facilitate clinical synthesis. Diverse etiological and neuropathological entities may produce clinical syndromes that are indistinguishable from one another; we know this is the case, for example, in PD [23]. This has led prior authorities to conclude that there is not one PD, and that the term ‘PDs’ would be more appropriate [23]. A similar issue is now raised with respect to ET [79].

The presence of heterogeneity across multiple domains (etiological, pathologic, age of onset, clinical features and clinical progression, pharmacological response phenotype, and possibly relationship with other diseases) strongly favors the notion that the etiological-pathological-clinical-therapeutic continuum that defines disease (fig. 1), and which occurs in ET, is not a single entity. Rather, there are likely to be several ETs. ET is thus likely to be a family of diseases for which the term ‘the ETs’ is more suitable and a more useful construct for future basic and pharmacotherapeutic investigations.

While one may question whether ET is no more than a syndrome, there is little evidence to support this. A syndrome is a set of symptoms that occur together (i.e. a symptom complex). For example, sore throat, coughing, sneezing, rhinorrhea, and malaise are a set of symptoms that often occur together, comprising an upper respiratory syndrome. In contrast with a syndrome, a disease is an entity characterized by a symptom complex as well as a specific course/prognosis (which may be variable), a specific etiology, and a set of organ-based changes in function or structure (whether known or unknown). For example, rhinoviral nasopharyngitis and influenza virus are diseases that are both characterized by an upper respiratory syndrome, yet the etiologies (i.e. infectious agents), clinical course, and tissue-based changes are distinct.

Action tremor of the arms, rather than ET, is perhaps syndromic. ET is an entity characterized by a symptom complex as well as a specific course/prognosis (which can be variable), a set of etiologies (many of which have not been specifically identified), and a set of organ-based

changes in function or structure (still under active investigation and discussion).

An important issue is whether this question really matters? As in PD [23], the answer is ‘yes’, as the question has implications for future research and clinical care. First, studies of disease etiology are less likely to identify disease risk factors if the case group in actuality consists of several rather than one disease. Indeed, a given risk factor, whether genetic or environmental, is likely to be specific to a particular one of the ETs. Similarly, studies of basic disease mechanisms will not benefit from this form of diagnostic misclassification. Disease mechanisms could be very different across members of the ETs. In the clinical domain, it would be important from a prognostic and disease course vantage point to know if one were dealing with a single entity or several. Finally, clinical trials and, in the future, neuroprotective trials for the ETs are destined to do poorly if we are lumping multiple diseases together under the term ‘ET’.

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