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Genetic mouse models of essential tremor: are they essential?

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The causative genes for essential tremor (ET), one of the most common genetic neurological disorders, have eluded scientists despite intensive search. Two gene loci linked to ET, one on chromosome 3q13 and another on chromosome 2p24.1, have been identified, and a missense mutation in the *HS1-BP3* gene on the 2p has been suggested as the cause of the disorder in about 10% of American ET patients. Therefore, the genetic basis for the vast majority of familial ET is still unknown. In this issue of the *JCI*, the gene coding for the γ-aminobutyric acid$_A$ (GABA$_A$) receptor α1 subunit is suggested as a potential candidate gene for ET, as mice lacking the gene express a phenotype that overlaps with some clinical characteristics of the human condition (see the related article beginning on page 774).

Essential tremor (ET), manifested by action tremor, present usually in the hands when arms are outstretched in front of the body but also involving mainly the head, vocal cords, and other parts of the body, is one of the most common neurological disorders. The prevalence of ET has been reported to range from 4% in a population aged 40 years or younger (1) to 14% in people 65 years or older (2). While it is generally recognized that ET is inherited in an autosomal-dominant pattern with high penetrance, no human gene mutations causing ET have yet been identified. Two ET loci, one on chromosome 3q13 (*ETM1*) (3) and another on chromosome 2p24.1 (*ETM2*) (4), have been isolated in families from geographically distinct areas. Recently, physical mapping of the *ETM2* region and systematic searching for gene mutations associated with the classic ET phenotype revealed a variation in the human homolog of the mouse HS1-binding protein 3 (HS1-BP3) gene (*Hs1bp3*) in 2 unrelated ET families (5). Since the HS1-BP3 protein is highly expressed in the cerebellum and regulates the Ca^{2+}/calmodulin–dependent protein kinase activation of tyrosine and tryptophan hydroxylase, it represents a viable candidate gene for the disorder. While this finding promises to provide insight into the patho-genesis of some types of ET, both the *ETM1* and *ETM2* loci have been excluded in other families, suggesting genetic heterogeneity. Not only does ET link to multiple gene loci, but the clinical expression of the condition is highly variable (6), and ET has also been associated with a variety of comorbidities, including dystonia, parkinsonism, malignant hyperthermia, migraines, and deafness (7). In addition, phenotypes resembling ET may appear in a variety of other disorders, such as Parkinson disease and a fragile X premutation (8). There is increasing reason, therefore, to believe that the clinical entity known as ET, in both its pure and *forme fruste* forms, arises from diverse etiologies.

Pathophysiology of ET

Anatomical and pharmacological pathways mediating ET may also be heterogeneous. Most physiological and functional imaging studies point to the involvement of cerebellar outflow circuitry in the pathophysiology of ET (9). The thalamus may also play a role in ET as high-frequency stimulation of the ventral intermediate nucleus of the thalamus produces a marked decrease in the amplitude of contralateral tremor (10). While the proposal that the neocortex is involved in ET is controversial (11), a familial postural tremor phenotypically similar to ET can be a rare manifestation of cortical reflex myoclonus (12). This "cortical tremor," which may or may not be accompanied by seizures, usually starts when the patient is between 19 and 30 years of age as tremulous finger movements and is often associated with a family history suggestive of ET. It is characterized by 8- to 15-hertz (Hz) synchronous, electromyographic bursts, each lasting 10–50 ms. The condition shares neurophysiologic features with myoclonus, including giant somatosensory evoked responses, and patients respond well to anticonvulsants such as clonazepam, primidone, and valproate, but the symptoms do not improve following treatment with β blockers, the treatment of choice for most patients with ET.

Animal models of ET

Animal models are important because they provide insights into the pathophysiology of human disease and may be useful in the development of novel drugs. At least 3 approaches have been used to produce tremor in animals: (a) administration of tremorgenic drugs such as harmaline; (b) lesioning of different subcortical structures; and (c) use of various inbred strains (13). However, only the single mutant gene models pinpoint potentially heritable causes of the disorder. Many of the mutant mouse tremor models described so far result in cerebellar degeneration and dysmyelinating phenotypes accompanied by a spectrum of ataxia, dystonia, weakness, and lethality. Given the shortage of human postmortem case material available for comparison, one inevitable difficulty in interpreting the relevance of these mouse models lies in deciding whether the tremor in each is indeed "essential."

GABA receptor and ET

In this issue of the *JCI*, Kralic et al. (14) describe a novel genetic model of ET in γ-aminobutyric acid$_A$ (GABA$_A$) receptor α1 subunit knockout (GABA$_A$ receptor α1$^{-/-}$) mice. GABA$_A$ receptors are a heterogeneous family of ligand-gated chloride channels, each composed of 5 protein subunits (2 α, 2 β, and 1 γ) encoded by 18 different genes. These channel subunits are differentially expressed in different regions, conferring a spectrum of pharmacological properties to synaptic inhibitory signaling throughout the central nervous system. Mice deficient in the α1 subunit display an action tremor, and Kralic et al. (14) propose that the mutant is a

Second, while some patients with ET exhibit subtle gait difficulties, the decreased ability of the mutant mice to remain on a rotating rod implies more significant vestibular or cerebellar incoordination. The latter discrepancy may partly reflect the fact that the homozygous knockout mice used in this study entirely lack GABA$_A$ receptor α1 subunits, whereas patients with a haploinsufficient condition would have the activity of this receptor subunit reduced by only one-half. In this case, one might still expect to see tremor without ataxia in heterozygous GABA$_A$ receptor α1$^{+/-}$ mice; however, these were not examined.

One example of indirect evidence that the GABA$_A$ receptor might be involved in ET is the observation that the anticonvulsant topiramate, which has multiple activities that may contribute to its neurostabilizing effects, including effects at sodium, calcium, and potassium channels, and at GABA$_A$ receptors, has been found to be effective in some patients with ET (16).

Animal models are windows into human diseases

In the most general sense, however, the GABA$_A$ receptor α1 knockout model is indeed essential, since knockout models of other GABA$_A$ receptor subunits (e.g., α5, α6, β2, β3, γ2,) do not display tremor, nor do models containing gene deletions impairing other steps in GABAergic transmission, including GABA synthesis (17). It is also interesting that deletion of the GABA$_A$ receptor α1 gene leads to tremor, since point mutations in the same and related subunits of this gene give rise to entirely different human phenotypes that lack tremor but induce epilepsy (18, 19).

Assuming that a subset of clinical ET disorders linked to defective GABAergic α1 subunit receptors is ultimately identified in humans, what does this new mouse model tell us about GABA neurotransmission and tremor circuitry? Can it help us localize the site and determine the onset of the excitability defect? Not easily. Since the GABA$_A$ receptor α1 subunit is normally switched on at birth and combines with other α, β, and γ subunits to form the pentameric ligand-gated chloride ion channel mediating GABAergic inhibition throughout the neuraxis, considerable analysis will be required to explain the highly selective mechanism for delayed-onset tremor.

The most prevalent GABA$_A$ receptor population in the brain is the pentamer containing subunits α1, α1, β, β, and γ (20). In the absence of the α1 subunit, alternative members of the α subunit family are substituted
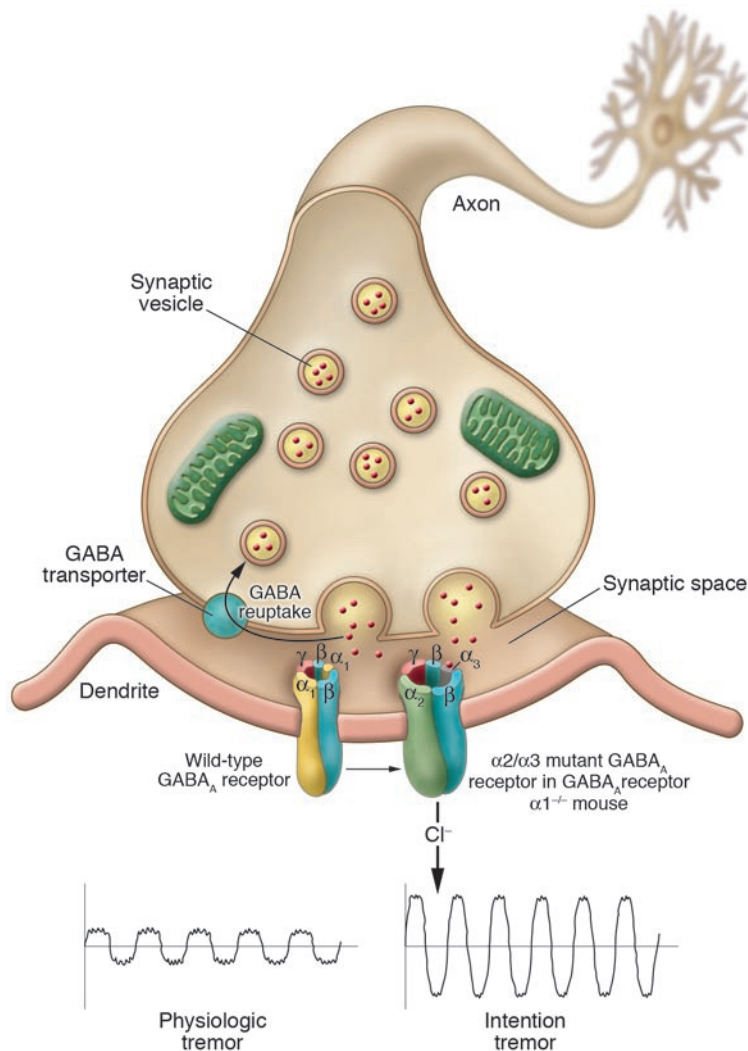

Figure 1
Molecular architecture of a GABAergic synapse showing alternative subunit switching in the GABA$_A$ receptor α1$^{-/-}$ mouse.

promising model of ET because the tremor is prominent in the limbs, is pronounced upon tail suspension yet absent when the mouse is relaxed, and improves with administration of primidone, propranolol, and ethanol — the 3 agents most consistently effective in the treatment of ET.

While these features closely resemble the symptoms described for common forms of the human disorder, several dissimilarities between the described phenotype in mice and typical human ET are also worth noting. First, the onset of the movement disorder in this mouse appears earlier in its development than the typical age of onset in human ET, although ET certainly can begin during childhood (15). Moreover, the reported appearance in mice of a pathologic tremor at a frequency of 19 Hz is substantially higher

than the 4- to 8-Hz tremor frequency typically observed in human ET. Since a continuous or gait-induced axial tremor of 10–14 Hz measured on the cage floor is typically seen in various drug-induced and single-gene mouse models of ET, the higher frequency (19 Hz) of the pathologic tremor described by Kralic et al. (14) is not simply due to the small size of the mouse, as the authors suggest. Instead, it is likely to be either an artifact of the in-air tail suspension recording technique or a specific characteristic of mice with the GABA$_A$ receptor α1 subunit deletion. Whether this difference represents a true disparity between neural oscillatory mechanisms or myokinetics in mice and humans must await the discovery and phenotypic description of a similar homozygous loss of function mutation of the human GABA$_A$ receptor α1 subunit.

in the cells where these receptors are normally expressed (Figure 1). This means that all remaining GABAergic transmission in the GABA_A receptor α1–deficient mouse relies upon a mixture of GABA_A receptors that in many cells are composed of novel α2–3/β, β/γ subunit combinations. Since these alternative receptors vary in kinetic behavior and pharmacology according to cell type and region, characterizing inhibitory transmission in the mutant nervous system will be a lengthy process, and the design of an effective drug to target this altered pattern may be dependent upon both age and region (21). The authors postulate that the tremor in GABA_A receptor α1$^{-/-}$ mice may result from a loss of GABA_A signaling by cerebellar purkinje cells but without actual degeneration of the cells (14). This would be consistent with the pathological studies in ET, which have so far not demonstrated microscopic cerebellar pathology in postmortem brains of patients with ET (22). It should be noted, however, that the GABA_A receptor α1 mutant mice have an overall reduction in brain size of about 15%, limiting the ability to directly attribute the tremor to this specific purkinje cell–signaling defect.

Conclusions

In summary, this new model of inherited tremor is welcome because it places GABA_A receptor α1, a well-known ligand-gated channel subunit, on the list of possible candidate genes for evaluation as a pathogenic cause of human ET and provides an excellent model for tracing the developmental cascade of signaling changes that lead to a tremulous phenotype. If the lessons learned from the investigation of other neurological disorders in mice are any guide, a human variant will soon be in hand; however, whether the human mutant will display tremor is not yet known. Only at that point can we comfortably conclude that the mouse mutant provides a truly "essential" model of the disorder.

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Illuminating the role of type I IFNs in colitis

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Recently, type I interferons IFN-α and IFN-β (IFN-α/β) have been evaluated in pilot clinical trials for the treatment of active ulcerative colitis. However, the underlying mechanisms that may contribute to a potential therapeutic effect are incompletely understood. A new study in this issue demonstrates a protective role for IFN-α/β, induced by activation of a Toll-like receptor 9–dependent pathway, in a rodent model of experimental colitis (see the related article beginning on page 695).

The pathogenesis of Crohn disease and of ulcerative colitis (UC), the 2 major forms of inflammatory bowel disease (IBD), involve a complex interplay among certain genetic, environmental, and immunological factors. Research in the last decade resulted in considerable progress in defining key inflammatory pathways in the inflamed gut and identifying new potential therapeutic targets. In particular, administration or manipulation of immunomodulatory cytokines have been proposed as alternative therapeutic strategies to modulate or inhibit proinflammatory cytokine production in IBD. Although, in the case of Crohn disease, novel strategies to inhibit TNF-α (e.g., administration of the anti–TNF-α monoclonal antibody, infliximab), IFN-γ, and IL-12 have been used in clinical trials (1, 2), relatively few successful studies using anticytokine agents for the treatment of UC have been performed. Recently, type I IFN-α