Chapter 6
Genetics of Primary Tremor Disorders

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Abstract Tremor, defined as rhythmical, involuntary oscillatory movement of a body part, is a symptom of numerous disorders of the central and peripheral nervous system. This chapter will deal with primary tremor disorders with a recognizable genetic component not discussed elsewhere in this book. These are essential tremor (ET), orthostatic tremor (OT), and cortical myoclonic "tremor." ET has a high genetic component and has been the subject of intense genetic investigation. Despite these efforts genes causing monogenic ET or genetic risk factors for genetically complex ET have not been reliably and reproducibly identified to date. OT is mostly a sporadic disease but has been described in sib pairs and identical twins. Cortical myoclonic "tremor" is characterized by irregular, rapid myoclonic jerks mimicking a tremor. Geniospasm (chin tremor) is also briefly discussed. Three loci and two putative candidate genes have been identified. In summary, the genetic investigation of tremor has been difficult and not overly successful up to now.

Keywords Tremor • Genetics • Essential tremor • Cortical tremor • Orthostatic tremor • Myoclonic epilepsy • Chin tremor • Geniospasm • ETM locus • FUS gene • Benign adult familial myoclonic epilepsy (BAFME) • Familial cortical myoclonic tremor with epilepsy (FCMTE) • Familial adult myoclonic epilepsy (FAME)

Introduction

Tremor, defined as rhythmical, involuntary oscillatory movement of a body part, is a symptom of numerous disorders of the central and peripheral nervous system. Tremor may either be the main symptom of a primary tremor disorder or one of the symptoms of other neurological diseases – many of them being movement disorders – defined by different main symptoms. The scope of this chapter will encompass only primary tremor disorders with a recognizable genetic component, i.e.,

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Table 6.1 Monogenic neurologic disorders commonly associated with tremor

Ataxia telangiectasia
Dystonia, monogenic forms
Hereditary peripheral neuropathies, monogenic forms
Hereditary spastic paraplegias, monogenic forms
Huntington disease
Neurodegeneration with brain iron accumulation (NBIA), monogenic forms
Parkinson disease, monogenic forms
Paroxysmal dystonic choreoathetosis
Spinal muscular atrophies
Spinobulbar muscular atrophy (Kennedy syndrome)
Spinocerebellar ataxias, monogenic forms
Wilson's disease

essential tremor (ET), orthostatic tremor (OT), cortical myoclonic tremor, and hereditary geniospasm. The genetics of dystonic tremor (in particular DYT1, DYT24, and DYT18 and others; see Chap. 7), the tremor of Parkinson disease (Chaps. 2 and 3), tremor associated with cerebellar ataxias (including fragile x-associated tremor/ataxia syndrome (FXTAS), see Chaps. 11 and 12), and other tremors associated with movement disorders (such as Wilson's disease (Chap. 14), hereditary spastic paraplegias (Chap. 16), mitochondrial disease (Chap. 18), etc.) will be dealt with in the respective chapters of this book. Table 6.1 presents a non-exhaustive list of the most common monogenic disorders associated with tremor.

Essential Tremor

Definition

ET, often referred to as "classic ET," is an idiopathic tremor syndrome, defined by a mainly postural and often also kinetic tremor of the hands, arms, and sometimes the head which is more accurately defined by a set of diagnostic criteria detailed in the section "Clinical phenotype and diagnostic criteria" [1].

Epidemiology

The term "essential tremor" has been coined in 1874 by the Italian physician Pietro Burresi, but the basic clinical phenotype has been described much earlier [2]. ET occurs worldwide. ET is a very common disorder, possibly the second most common movement disorder after restless legs syndrome (RLS), and the prevalence is increasing due to an aging population [3]. Estimates vary considerably, but a prevalence of

~1 % in the general population and ~5 in the population older than 65 years is a reasonable estimate [4]. ET might be slightly more common in men compared to women (~1.1 times) [4]. The age of onset of ET varies widely from childhood to senescence. It is not entirely clear whether the age of onset of ET shows a unimodal distribution with an age-dependent increase of the incidence or a bimodal distribution with a young-onset peak around 20 years of age and another peak centered around 60 years of age [5–7]. The young-onset peak has been attributed to the fact that many studies were done in tertial referral centers [6]. However, our own unpublished data in a sample of 913 ET patients mostly recruited via newspaper articles supports the notion of a young-onset peak mostly attributable to patients with a positive family history. It is unknown whether ET has an impact on life expectancy [8, 9]. One Spanish/US study addressed this issue and found a small but statistically significant reduction of life expectancy in ET patients [9]. However, this study examined an aged population with a mean age at inclusion of 74 years. After stratification for tremor duration in long (>5 years) and short (<5 years), a reduction in life expectancy was observed only in the short tremor duration group. These patients had a senile onset of tremor, and it is currently unknown if this form of tremor is etiologically comparable to ET or represents a separate "senile tremor" entity.

Clinical Phenotype and Diagnostic Criteria

ET is probably best defined looking at a four slightly different but widely overlapping sets of diagnostic criteria proposed in the last 20 years. The first set of criteria was published by a specialist subgroup of the Movement Disorders Society (MDS), the Tremor Investigation Group (TRIG) in 1995 [10]. The core feature is a "bilateral postural tremor with or without kinetic tremor, involving hands and forearms, that is visible and persistent." Exclusion criteria for "definite" and "probable" ET are other causes of tremor and additional neurological signs except "increased resistance to passive movements of a limb about a joint upon voluntary activity of another body part" (Froment's sign). In addition a tremor duration of >5 years for "definite" and >3 years for "probable" ET is required. "Possible" Et allows for a number of other neurologic signs or a concomitant neurologic disorder, e.g., parkinsonism or dystonia. The second set of criteria proposed in 1998 by the MDS discards the duration criterion and differentiates between "classic" ET, encompassing "definite" and "probable" ET according to the TRIG criteria and – unchanged – "possible" ET [1]. The third set of criteria by essentially the same authors proposes "core" and "secondary" criteria [11]. In addition to the tremor of the hands, an isolated tremor of the head is listed among the core criteria, and a cogwheel phenomenon is generally permitted. A fourth set of diagnostic criteria, the Washington Heights-Inwood Genetic Study of Essential Tremor (WHIGET) criteria, were published in 1997 [12]. These criteria are similar to the previously described ones but include tremor amplitude criteria while lacking some of the criteria of the aforementioned diagnostic criteria.

Table 6.2 Summary of diagnostic criteria for ET

Core criteria
1. Bilateral postural and kinetic tremor of the hands and forearms (but not rest tremor) (T, MD, B)
2. Absence of other neurologic signs (T, MD, B), with the exception of the cogwheel phenomenon (T, B)
3. May have isolated head tremor with no signs of dystonia (MD, B)
Duration and level of certainty
1. "Definite ET": duration >5 years + comprehensive exclusion of other causes + no stepwise deterioration (T)
2. "Probable ET": duration >3 years + same criteria as "definite ET" (T)
3. "Possible ET": no duration criterion + type I, some other neurologic symptoms allowed; type II, monosymptomatic or isolated tremors of uncertain relation to essential tremor (T)
Secondary criteria
1. Positive family history (present in 30–60 % of patients) (B)
2. Beneficial alcohol response (present in 50–75 % of patients) (B)

According to TRIG (T, [10]), Movement Disorders Society (MD, [1]) and Bain et al. (B, [11])

Table 6.2 summarizes the key features of the three sets of criteria created by task forces of the MDS.

The tremor amplitude in ET patients usually increases, while the tremor frequency decreases with advancing age. Patients with mild ET rarely show a significant rest tremor, while ~10–15 % of patients with advanced ET show a mild rest tremor. The tremor in ET patients with rest tremor is – in contrast to PD – not suppressed but enhanced upon voluntary movement [13]. While older studies emphasize the preponderance of a postural tremor in ET, more recent studies often report an increase of the tremor upon (goal-directed) movement [14]. The kinetic tremor is a gait disturbance in advanced ET, and kinematic analyses demonstrate cerebellar dysfunction in ET [15]. Ethanol ameliorates the tremor in many ET patients [16]. Up to now ethanol sensitivity has not been sufficiently studied to determine whether it might serve as a useful diagnostic marker. The full differential diagnosis of ET comprises a large number of diseases, but only few of these are commonly encountered. The tremor frequency in ET is mostly in the 4–8 Hertz (Hz) range but might be up to 12 Hz. Physiologic tremor and enhanced physiologic tremor present with a frequency in the 8–12 Hz range and might be difficult to distinguish from mild ET in the upper frequency range [17]. A common condition exacerbating physiologic tremor is hyperthyroidism. The relationship between dystonia and ET is a longstanding matter of debate [18]. While dystonia is an exclusion criterion in the different sets of diagnostic criteria, many clinicians would regard mild, subclinical signs of dystonia, mostly not recognized by the patients who complain of tremor as being compatible with ET. This problem is most pronounced in studies of familial ET because a closer examination of all family members often reveals mild dystonic signs in conjunction with obvious tremor in a subset of family members [19, 20]. It is unclear whether these individuals suffer from dystonic tremor or from ET with a dystonic component. Tremor-dominant PD is in most cases differentiated by a preponderant rest tremor and additional neurologic signs in PD patients. Drug-induced

Table 6.3 Additional clinical features possibly associated with ET

Cognitive deficits (frontal executive and memory)
Dementia
Personality changes
Depression
Mild olfactory dysfunction
Hearing impairment
Increased mortality

tremor should be ruled out by an appropriate drug history. Psychogenic tremor can be difficult to differentiate from ET [21].

A number of additional clinical features have been reported in ET patients (Table 6.3). Most of these features are relatively mild and therefore subclinical. Keeping in mind that ET might be an etiologically heterogeneous group of biologically different diseases, it is not clear whether the reported features affect only certain subgroups or all ET patients. Some of the studies reporting additional features studied only ET with an age of onset >65 years, e.g., [22, 23]. Whether these patients represent a distinct subform of "senile (essential) tremor" is unknown. Therefore, these results might not be completely applicable to young-onset ET patients. Clarifying these issues would require an extremely large and very long-term prospective study. An association between ET and Parkinson disease (PD) has been analyzed by numerous studies which show inconsistent results.

Etiology and Pathogenesis

Genetic and environmental factors play a role in the etiology of ET. Environmental risk factors might be harmane and lead. Both substances have been found in higher concentrations in the serum of ET patients compared to controls [24, 25]. Harmala alkaloids are potent tremor inducers in rodents. Two hypotheses regarding the pathogenesis of ET exist. One hypothesis, mainly based on neurophysiological data states that ET is a neurofunctional disorder caused by abnormal oscillations in the corticobulbo-cerebello-thalamo-cortical loop which is also involved in the generation of other tremor forms [26]. The other hypothesis, based on autopsy findings, states that ET is a neurodegenerative disorder, mainly involving the cerebellum [27]. However, in the published autopsy studies, all ET patients were very old at the time of autopsy and the pathological changes were mild compared to other neurodegenerative disorders. In addition, these findings have not been replicated by other groups [28].

Heritability

ET patients can tentatively be separated into at least two subgroups. Predominantly young-onset patients (onset <~40–50 years) with a strongly positive family history suggesting monogenic, mostly autosomal dominant inheritance form one subgroup,

while sporadic patients, often with a higher age of onset, form the other subgroup [22, 29, 30]. It is currently not clear whether patients with a very high age at onset (>~65–75 years) form a third subgroup which could be termed "senile tremor" [31, 32]. Heritability of sporadic ET has been assessed using family history and twin studies. A number of studies have shown that family history studies in ET are unreliable and tend to underestimate the genetic component. Twin studies are a better way to estimate heritability [33–35]. Two twin studies of ET have been conducted – one in a US population and the other one employing the Danish twin registry [36, 37]. The US study found a pairwise concordance rate of 0.60 (United States, definite ET), whereas the Danish/German study one of 0.93 (Denmark/Germany, definite and probable ET) for monozygotic twins versus 0.27 (United States) and 0.29 (Denmark/Germany) for dizygotic twins which translate into rough heritability estimates between 45 and 90 %.

Molecular Genetics

Presumably Monogenic ET

Linkage Studies. Three chromosomal loci have been identified for presumably monogenic ET using genome-wide linkage analysis. The results of genome-wide linkage scans are usually expressed as logarithm of odds (LOD) scores. In monogenic disorders an LOD score >3.3 in a single family is regarded as conclusive, while an LOD score >2 is usually regarded as suggestive for a novel locus and as confirmatory for a known locus.

ETM1 was mapped to chromosome 13q13 in 16 small Icelandic families [38]. The maximum LOD score in a single family was 1.42, the maximum LOD score across all families was 3.71. Eight follow-up studies were not able to confirm the locus [39–46]. Co-segregation of the Gly allele of the dopamine receptor 3 gene (*DRD3*) Ser9Gly (rs6280) polymorphism located in the ETM1 locus was observed in 23 out of 30 French families with 1–5 affected individuals and showed a weak association of the same polymorphism with ET in sporadic US ET patients [47]. Three follow-up studies found co-segregation of the Gly allele in 8/46 families of varying size which is not surprising considering an allele frequency of the Gly allele of rs6280 ranging from 0.3 (dpSNP database, Asian) to 0.5 (Exome Sequencing Project database) [44, 48, 49]. Out of six association studies attempting replication between rs6280 and ET, only one yielded a significant *p*-value [44, 48–52]. Therefore, it is questionable whether ETM1 harbors a gene causing monogenic ET. It also seems unlikely that the *DRD3* polymorphism rs6280 is a major risk factor for sporadic ET.

The *ETM2* locus has been convincingly mapped to chromosome 2p24 in a very large Czech/American family with a conclusive LOD score of 5.92 [53]. Eight follow-up analyses of 34 additional families with 3–19 affected individuals did not confirm these results [40, 42–46, 54]. The group that mapped the locus described a

genetic variant (Ala265Gly) in the hematopoietic lineage cell-specific protein binding protein 3 (*HS1BP3*) that segregated with ET in two families, one of them containing 10 affected family members [55]. It is not reported if this variant has been analyzed in the original family which allowed mapping of the locus. Out of two association studies, one found association between the *HS1BP3* variant and ET and one did not [56, 57]. The ETM2 locus is based on a convincing linkage result in one large family and could well harbor a gene for monogenic ET, but it is unlikely that the Ala265Gly variant in the *HS1BP3* gene is causative.

The *ETM3* locus has been mapped to chromosome 6p23 in one large American family with a nonconclusive maximum LOD score of 2.93 [20]. The LOD score was obtained in an "affected-only" analysis. The published pedigree shows that – if this locus harbors a gene for monogenic ET – a very low penetrance and extremely high phenocopy rate of ~20 % has to be postulated. In a second family, co-segregation of markers in the ETM3 region was shown but LOD scores were below 2 [20]. Four independent follow-up studies examining 21 additional families with 3–15 affected individuals were not able to demonstrate linkage to this locus in any of the families [39, 40, 43, 44].

Exome sequencing, the DNA sequencing of all protein coding exons in the genome, is a novel method made possible by the rapid advances in DNA sequencing technology, collectively called "next-generation sequencing" (NGS). A Canadian group identified a stop mutation in the fused in sarcoma (*FUS*) gene in a large Franco-Canadian family [58]. The mutation segregated well with the ET phenotype in the family. Follow-up studies identified a number of additional mutations in *FUS* in sporadic and familial ET patients [59–63]. However, it is not clear whether the frequency of these mutations exceeds the mutation frequency of *FUS* in controls. In order to confirm the causative role of *FUS* further, large ET families showing co-segregation of *FUS* mutations with ET are needed.

Genetically Complex ET

Currently the method of choice for the analysis of genetically complex disorders is the genetic association study. Genetic association studies are usually conducted either as candidate gene studies or as genome-wide association studies (GWAS).

Candidate gene association studies in ET were not successful, and none of the associations found in these studies have been consistently replicated [64]. They will therefore not be discussed in detail. Candidate gene selection followed different approaches: (1) assuming a pathogenetic overlap between ET and PD (genes studied: *SNCA*, *LRRK2*, *MAPT*, *GBA*, Parkin); (2) a number of short-tandem-repeat (STR) expansions analyzed because anticipation has been observed in some families with ET (genes/repeats studied: *FMR1*, *PP2APR55beta*, *C9orf72*, *ATX2*, *MJD1* repeat expansions were analyzed and the "repeat-expansion-detection" (RED) method was used for the detection CAG expansions); and (3) genes acting in the gamma-amino-butyric-acid (GABA) neurotransmitter system. GABA is the most important inhibitory neurotransmitter in the central nervous system and most likely

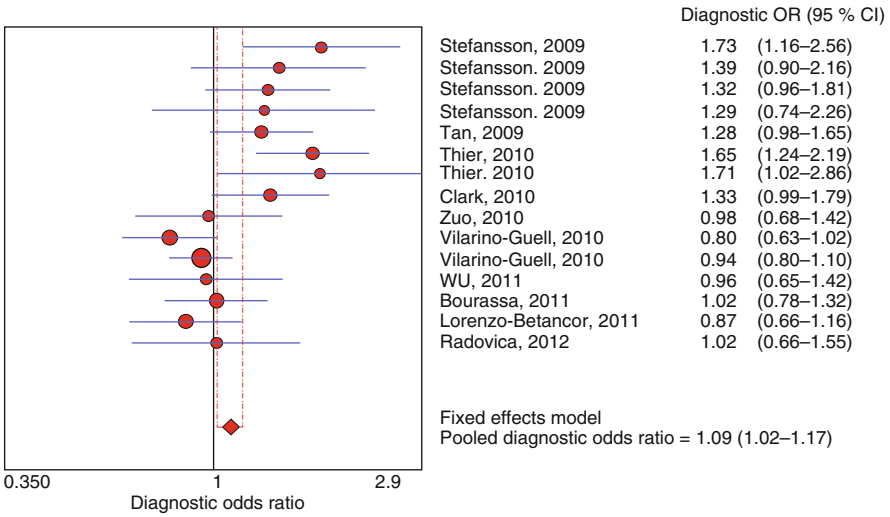

Fig. 6.1 Meta-analysis of the association between LINO1 rs9652490 and ET

involved in the pathogenesis of ET. GABA receptor alpha 1 subunit-deficient mice exhibit a spontaneous tremor; a GABAergic deficit has been demonstrated in ET patients by positron emission tomography (PET), and autopsy findings in ET patients suggest that the GABA receptor density is reduced in the dentate nucleus of the cerebellum [65–67]. Unfortunately, four studies investigating numerous genes in the GABA system were negative, and GWAS studies did not highlight GABA-related genes either [68–70]. It needs to be mentioned that most candidate gene association studies suffered from relatively small sample sizes and were therefore not able to reliably exclude weak to moderate associations.

Genome-wide association studies (*GWAS*) examine a large number of genetic markers which are distributed over the whole genome. GWA studies are usually regarded as conclusive if they fulfill the following requirements: (I) a two-stage design with a discovery stage and a replication stage, (II) achieving "genome-wide significance" in the discovery stage, (III) obtaining *p*-values in the replication stage which remain significant after Bonferroni correction, and (IV) replication in different patients samples in independent laboratories.

Two GWAS of ET have been performed to date. The first GWAS study by the Icelandic deCODE consortium found an association between ET and a single nucleotide polymorphism in the leucine-rich repeat and Ig domain containing 1 gene (*LINGO1*) which did not reach genome-wide significance in the discovery stage (SNP, rs9652490, $p = 3.0 \times 10^{-7}$) but was significant in the replication stage ($p = 0.0010$) [71]. Subsequent independent replication studies showed mixed results. The result of a meta-analysis of all available studies for SNP rs9652490 excluding the discovery cohort is shown in Fig. 6.1 (pooled odds ratio, 95 % confidence interval, 1.09 (1.02–1.17)) [71–81]. One study reported association with the opposite allele of the one found to be associated in the initial Icelandic study, leading to

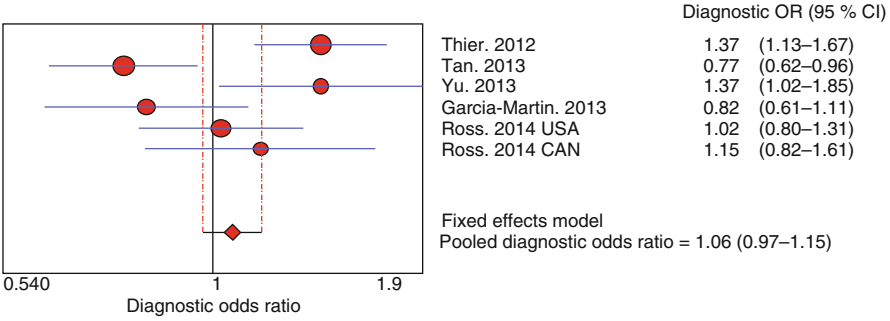

Fig. 6.2 Meta-analysis of the association between SLC1A2 rs3794087 and ET

substantial interstudy heterogeneity [78]. A second SNP in the same gene (rs11856808) found in the Icelandic study did not reach significance in most replication studies [71]. *LINGO1* is a signaling molecule in the NOGO receptor pathway and regulates neuroregeneration and neuronal survival in a negative way [82]. Recently two studies reported increased *LINGO1* expression in the cerebellum of ET patients [83–85].

The second GWAS conducted in a German/Austrian/Danish ET sample identified an SNP (rs3794087) in the solute carrier family 1 member 2 gene (*SLC1A2*) which did not reach genome-wide significance in the discovery stage ($p = 6.95 \times 10^{-5}$) but was significant in the replication stage ($p = 1.25 \times 10^{-3}$) [86]. This study included only patients with "probable" and "definite" ET according to the TRIG criteria. *SLC1A2* encodes the excitatory amino acid transporter 2 (EAAT2), the major transporter limiting the action of the excitatory transmitter glutamate in the brain [87–90]. Up to date, four studies attempting replication with mixed results have been published. A meta-analysis of all studies shown in Fig. 6.2, again without the discovery sample, does not support an association between the rs3794087 and ET (pooled odds ratio, 95 % confidence interval, 1.09 (0.97–1.15)) [86, 91–94].

In summary it has not been possible to identify beyond doubt any genetic cause or risk factor of ET despite a high heritability shown in multiple studies.

Primary Orthostatic Tremor

Primary orthostatic tremor is a very rare disorder of unknown etiology and pathogenesis characterized by a high-frequency (13–18 Hz) tremor of the legs when standing, ameliorated or disappearing when walking and not present when sitting or lying [95]. The condition has also been described in conjunction with Parkinson disease. Although primary orthostatic tremor has been described mainly in sporadic patients, three reports of affected sibs exist, one of them in a brother/sister pair [96], one in male monozygotic twins [97], and one in three brothers [98]. The parents of

the patients – except for anecdotal evidence concerning the mother in one study – were not affected by primary orthostatic tremor suggesting either autosomal recessive inheritance or, in the families with male patients only, X-linked inheritance. The molecular genetic basis of primary orthostatic tremor has not been investigated.

Cortical Myoclonic Tremor

Cortical myoclonic tremor designates a group of rare, mostly autosomal dominant, genetically heterogeneous disorders characterized by similar clinical features, comprising an irregular, high-frequency myoclonus of cortical origin mimicking an irregular tremor and in most patients epileptic fits of different semiology and interictual EEG abnormalities [99]. A large number of synonymous acronyms have been coined for these disorders including autosomal dominant cortical myoclonus and epilepsy (ADCME), benign adult familial myoclonic epilepsy (BAFME), familial cortical myoclonic tremor with epilepsy (FCMTE), and familial adult myoclonic epilepsy (FAME). The first symptom of the disease is in most cases an "irregular action tremor" of the upper limbs [99]. Polymyography shows arrhythmic high-frequency burst-like discharges of very short duration (50 ms), typical for cortical myoclonus [100, 101]. The cortical origin of the myoclonus was confirmed with EEG-EMG coherence and EMG functional MRI studies [100, 101]. In addition features of cortical reflex myoclonus, e.g., giant somatosensory-evoked potentials (g-SEP) and abnormalities of the long loop reflexes (LLR) suggesting cortical hyperexcitability, are found [100–102]. A number of additional clinical features suggesting involvement of the cerebellum (e.g., eye movement abnormalities, gait ataxia) and slowly progressive cognitive decline in some families have been described. Neuropathologic data are very scarce. Published autopsy data suggest cerebellar degeneration with Purkinje cell loss [100]. Three loci for cortical myoclonic tremor have been mapped. *FAME/BAFME 1* was mapped to chromosome 8q23.3-q24.11 in Japanese families with conclusive LOD scores [103, 104]. This entity seems to have a later age of onset and milder course than the other loci which were mapped in European families. *FAME/BAFME 2* was mapped with conclusive LOD scores to chromosome 2p11.1-q12.2 in a number of Italian families [102, 105, 106]. *FAME/BAFME 3* was mapped to chromosome 5p15.31-p15.1 in a large French family with a conclusive maximum LOD score of 6.3 [107]. A fourth locus (*FAME/BAFME 4*) has been mapped with a maximum LOD score of 5.4 to chromosome 3q26.32-q28 in a Thai family [108]. Recently a similar phenotype involving myoclonic tremor and epilepsy with autosomal recessive inheritance has been described in a consanguineous Egyptian family [109]. The clinical features showed clear differences compared to the previously described families with autosomal dominant inheritance. All patients experienced focal temporal lobe seizures as manifesting symptom, and the SEP were normal. MRI revealed temporal mesial sclerosis in one patient. The underlying genetic defect was mapped using homozygosity mapping to chromosome 1q31-q32.2 with a conclusive LOD score of 3.6 and three

possibly deleterious rare variants in the genes *DDX59* probably encoding an RNA helicase with very low expression in the brain; *TNNI1*, a gene implied in slow-twitch skeletal muscle contraction, and *CNTN2* (*Contactin 2*), a neuronal membrane protein, were found in the homozygous state in all 5 patients and in the heterozygous state in the parents [109], and *CNTN2* was highlighted as the most likely causal gene. Another putatively causal gene was identified in a Spanish family with presumably autosomal dominant cortical myoclonic tremor using whole-exome sequencing [110]. Two possibly deleterious rare variants showing full co-segregation with the disease in the available family members were identified, one in the tumor suppressor gene *MYBBP1A* and the other one in the *ACMSD* gene encoding an enzyme involved in the kynurenine pathway of tryptophan degradation [110]. Based on the fact that the kynurenine pathway has been shown to be involved in the pathogenesis of neurological disorders including epilepsies, the *ACMSD* gene was highlighted as the most likely causal gene. *ACMSD* maps to chromosome 2q21.3 outside the FAME/BAFME 2 locus.

In summary five chromosomal loci (4 AD, 1 AR) for cortical myoclonic tremor have been mapped with conclusive LOD scores in at least one family. Two candidate genes – *CNTN2* and *ACMSD* – have been identified, but none of the gene findings have so far been replicated.

Hereditary Geniospasm

Hereditary geniospasm is a rare, autosomal dominant, early onset, often stress-induced involuntary tremulous movement of the skin overlying the chin ("trembling of the chin") already observed at the end of the nineteenth century [111]. The disease is usually not associated with other neurologic abnormalities and is not progressive. Around 25 families have been described in total. Botulinum toxin is the therapy of choice. Hereditary geniospasm has been mapped to chromosome 9q13-q21 with a conclusive maximum LOD score of 5.24 in a large British family [112]. The underlying genetic defect is unknown. The 9q13-q21 locus was excluded in another family from Canada suggesting genetic heterogeneity of the disease [113].

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