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Review

Rational search for genes in familial cortical myoclonic tremor with epilepsy, clues from recent advances

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ABSTRACT

Familial cortical myoclonic tremor with epilepsy (FCMTE) is an autosomal dominant epilepsy syndrome with considerable clinical and genetic heterogeneity. The most important clinical manifestations include adult onset, cortical myoclonic tremor, with or without epileptic seizures. Of the four loci reported, which included 8q24 (FCMTE1), 2p11.1-q12.2 (FCMTE2), 5p15.31-p15.1 (FCMTE3), and 3q26.32-3q28 (FCMTE4), only one probably causative mutation was found co-segregated in two FCMTE2 pedigrees in the α_2-adrenergic receptor subtype B (*ADRA2B*) gene. In this review we discuss studies that focused on the molecular genetics of FCMTE, its neuropathology, clinical, neurophysiological and neuroimaging features, which may offer useful clues for the search for causative FCMTE genes. Next-generation sequencing has identified many causative genes in monogenic diseases. However, most next-generation sequencing applications focus on detecting single nucleotide variants or small insertions/deletions, which do not completely resolve the challenge of identifying causative genes in FCMTE. Recent progress in exploring FCMTE has revealed that special mutations such as copy number variants, exon rearrangements and large trinucleotide repeat expansion (or polynucleotide repeat expansion) should be considered. Clues from neuropathological, clinical, neurophysiological and neuroimaging studies indicate that the candidate causative genes should be expressed in the cerebellum, especially in Purkinje cells, and be associated with calcium signaling and GABA receptors. We propose that the developing novel algorithms of next-generation sequencing data, which could detect structure variants and candidate causative gene selection when combined with special mutations detection analysis represent possible future direction of a rational search for causative genes in FCMTE.

1. Introduction

Familial cortical myoclonic tremor with epilepsy (FCMTE), which is widely known as benign adult familial myoclonic epilepsy (BAFME) in Japan, and autosomal dominant cortical myoclonus and epilepsy (ADCME) in Europe, was first reported in the 1980s in the Japanese population with an autosomal dominant condition [1,2].

FCMTE is also described under many other terms including familial adult myoclonic epilepsy (FAME), familial cortical myoclonic tremor (FCMT), familial cortical tremor with epilepsy (FCTE), familial essential myoclonus and epilepsy (FEME), familial benign myoclonus epilepsy of adult onset (FMEA) and heredofamilial tremor and epilepsy (HTE).

The most important clinical manifestations include adult onset, cortical myoclonic tremor (CMT), with or without epileptic seizures that mainly manifest as generalized tonic-clonic seizures (GTCS). CMT is usually the first symptom (mean age at onset is 35 years, range 10–60 years), and is characterized by tremulous finger movements and myoclonus of the extremities, which are increased by action and posture [2].

Electromyography (EMG) can detect giant somatosensory evoked potential (g-SEP) and long-latency cortical reflex (C-reflex) in affected members, which collectively support the cortical origin of CMT [2]. Most antiepileptic drugs, especially clonazepam and valproic acid were reported to improve both CMT and GTCS. However, a potentially severe and life-threatening situation was reported in FCMTE patients with use of gabapentin [3]. Based on clinical and electrophysiological grounds, van Rootselaar et al.

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proposed that BAFME, ADCME, FAME, FCMT, FCTE, FEME, FMEA, and HTE should be regarded as integral components of one disease spectrum named as FCMTE and a diagnostic criterion for FCMTE was subsequently proposed [2]. With the identified clinical and electrophysiological features, FCMTE is a well-defined epilepsy syndrome that still awaits nosological placement in the International League Against Epilepsy (ILAE) classification [4].

Four loci were identified including 8q24 (FCMTE1), 2p11.1-q12.2 (FCMTE2), 5p15.31-p15.1 (FCMTE3) and 3q26.32-3q28 (FCMTE4), and several possibly/probably causative genes were also reported (see Tables 1 and 2). However, a significant gap remains between the real causative genes and FCMTE [5–21]. Herein, we have reviewed previous molecular genetic studies of FCMTE and associated advances in neuropathological, clinical, neurophysiological and neuroimaging studies. We aim to provide possible explanations for the difficulties of previous studies to identify causative genes of FCMTE, and to offer future directions for the search for causative genes of FCMTE.

1.1. Recent advances in the identification of causative gene region

FCMTE pedigrees were previously reported in Japan, Italy, France, Thailand, Spain and China with considerable genetic heterogeneity. Great effort has been made recently, and four loci including 8q24 (FCMTE1), 2p11.1-q12.2 (FCMTE2), 5p15.31-p15.1 (FCMTE3) and 3q26.32-3q28 (FCMTE4) have been identified (see Table 1) [5–22].

FCMTE1 (OMIM 601068) was the first locus that identified in a large pedigree (i.e., FCMTE1 No.1), and four small pedigrees (i.e., FCMTE1 No.2–5) from Japan. Plaster et al. localized four small pedigrees (i.e., FCMTE1 No.2–5) to a relatively small region (i.e., a 4.6 cM interval from D8S514 to D8S1804) in 1999 [6]. However, we noticed that in the five microsatellite markers (i.e., D8S514, D8S1826, 572-18, D8S384 and D8S1804) they chose for haplotype analysis, the physical positions of D8S384, D8S514 and D8S1826 should be chr8: 118456019–118456384, chr8: 123742103–123742461 and chr8: 123856163–123856442. The position of microsatellite markers above were mixed in an incorrect array due to limited information at that time. Herein, we have analyzed their haplotype and identified that the downstream boundary of causative gene region was D8S514. The large pedigree of FCMTE1 (i.e., FCMTE1 No.1) was firstly localized to an 8 cM interval (i.e., between D8S1784 and D8S1694) by Mikami et al. in 1999 [5]. Mori et al. remapped the causative gene region to a 7.16 Mb interval (i.e., between rs1898287 and rs2891799) in FCMTE1 No.1 pedigree. Sanger sequencing and copy number variants (CNVs) analysis failed to identify any causative mutation in this 7.16 Mb interval in FCMTE1 No.1 pedigree [7]. Recently, Cen et al. reported a Chinese FCMTE1 pedigree (i.e., FCMTE1 No.6), which was also localized on 8q22.3-q24.13. Whole-exome sequencing (WES) was performed and a single nucleotide variant (SNV) in the *SLC30A8* gene was co-segregated in the pedigree. However, evidence supporting the *SLC30A8* gene as the causative gene of FCMTE1 was insufficient [8].

FCMTE2 (OMIM 607876) was the most widely reported type of FCMTE and most of the FCMTE2 pedigrees came from European countries (i.e., FCMTE2 No.1-11). Licchetta et al. narrowed the causative gene region to a 10.4 Mb interval (i.e., between D2S181 and D2S2311) by reviewing previous reports of the localization of FCMTE2 pedigrees [17]. Dozens of candidate genes in FCMTE2 locus have been screened and only one probably causative mutation in the *ADRA2B* gene was co-segregated in two pedigrees (i.e., FCMTE2 No.1 and No.11), which shared a common ancestor [18]. No SNVs, small insertions/deletions (indels), or large indels in the *ADRA2B* gene was detected in the other two FCMTE2 pedigrees (i.e., FCMTE2 No.4 and No.6) [18]. Until now, no other mutation in *ADRA2B* has been reported in other FCMTE pedigrees. These indicate that additional evidence is needed to confirm whether or not *ADRA2B* is the authentic causative gene in FCMTE2 locus, while the search for a second causative gene in this locus is still formally possible.

FCMTE3 (OMIM 613608) was reported in a French pedigree (i.e., FCMTE3 No.1) and a Chinese pedigree (i.e., FCMTE3 No.2) [19,20,22]. Sanger sequencing of two candidate genes (*SEMA5A* and *CTNND2*) in FCMTE3 No.1 pedigree did not detect any causative mutation [18]. FCMTE4 (OMIM 615127) was only reported in a Thai pedigree (i.e., FCMTE4 No.1) without causative gene identified [21].

Although next-generation sequencing (NGS) like WES and whole-genome sequencing (WGS) can detect the causative mutation without causative gene regional information, localization of causative gene remains very important in causative gene

Table 1
Reported loci and their pedigrees of FCMTE.

Clinical type OMIM No.	Reference	Origin/Pedigree No.	Causative gene region	Gene
FCMTE1	[5]	JPN/No.1	8q23.3-q24.11	Unknown
OMIM 601068	[6]	JPN/No.2-5	8q24.13	Coding region of "Kv8.1" gene excluded
	[7]	JPN/No.1	8q24.11-q24.13	SNVs and SIDs in all exons of 38 genes in this region excluded by SS
	[8]	CHN/No.6	8q22.3-q24.13	One SNV in *SLC30A8* by NGS
FCMTE2	[9]	ITA/No.1	2p11.1-q12.2	Unknown
OMIM 607876	[10]	ITA/No.2,3	2p11.1-q12.2	Unknown
	[11,12]	ITA/No.4,5	2p11.1-q12.2	Unknown
	[13]	ITA/No.6	2p11.1-q12.2	Unknown
	[14]	SPA/No.7	2p11.1-q12.2	SNVs and SIDs of *SIAT9*, *KCNIP3*, *REEP1*, *VAMP5* and *DRD5P1* excluded by SS.E-Rs of *REEP1* and *DRD5P1* excluded by MLPA
	[15]	ITA/No.8	2p11.1-q12.2	Unknown
	[16]	AUS&NZL/No.9	2p11.1-q12.2	Unknown
	[17]	ITA/No.10	2p11.1-q12.2	Unknown
	[18]	ITA/No.1,11	2p11.1-q12.2	One SID in *ADRA2B* detected in No.1 and No.11 pedigrees by NGS and SS. No SNVs, SIDs or large indels of *ADRA2B* was detected in No.4 and No.6 pedigrees.
FCMTE3	[19]	FRA/No.1	5p15.31-p15	SNVs and SIDs of *SEMA5A* and *CTNND2* were excluded by SS
OMIM 613608	[20]	CHN/No.2	5p15.31-p15.1	Unknown
FCMTE4OMIM 615127	[21]	THA/No.1	3q26.32-q28	Unknown

JPN, Japan; ITA, Italy; SPA, Spain; AUS, Australia; NZL, New Zealand; FRA, France; CHN, China; THA, Thailand; SNVs, single nucleotide variants; SIDs, small insertions/deletions; SS, Sanger sequencing; E-Rs, Exon rearrangements; MLPA, multiplex ligation dependent probe amplification; NGS, next-generation sequencing.