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The ACMSD gene, involved in tryptophan metabolism, is mutated in a family with cortical myoclonus, epilepsy, and parkinsonism

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Abstract

Familial cortical myoclonic tremor and epilepsy is a phenotypically and genetically heterogeneous autosomal dominant disorder characterized by the presence of cortical myoclonic tremor and epilepsy that is often accompanied of additional neurological features. Despite the numerous familial studies performed and the number of loci identified, there is no gene associated with this syndrome. It is expected that through the application of novel genomic technologies, such as

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whole exome sequencing and whole genome sequencing, a substantial number of novel genes will come to light in the coming years. In this study, we describe the identification of two disease-segregating mutations in a large family featuring cortical myoclonic tremor with epilepsy and parkinsonism. Due to the previous association of ACMSD deficiency with the development of epileptic seizures, we concluded that the identified nonsense mutation in the *ACMSD* gene, which encodes for a critical enzyme of the kynurenine pathway of the tryptophan metabolism, is the disease-segregating mutation most likely to be responsible for the phenotype described in our family. This finding not only reveals the identification of the first gene associated with familial cortical myoclonic tremor and epilepsy but also discloses the kynurenine pathway as a potential therapeutic target for the treatment of this devastating syndrome.

Keywords

FCMTE; Whole Exome Sequencing; ACMSD; Kynurenine Pathway

Introduction

Familial cortical myoclonic tremor and epilepsy (FCMTE), also known as BAFME, FAME, FEME, FCTE, and ADCME, is an autosomal dominant disorder characterized by adult-onset cortical myoclonus, rare epileptic seizures, benign course, and beneficial response to antiepileptic drug therapy; cerebellar ataxia, dementia, and marked photosensitivity may also manifest [1, 2]. Myoclonus is usually the first symptom and is characterized by tremulous finger movements and myoclonus of the extremities [3]. Although diagnosis is made based on clinical and electrophysiological criteria, FCMTE might be misdiagnosed of essential tremor (ET) or progressive myoclonus epilepsy (PME). To avoid confusion and possible misdiagnosis of patients, van Rootselaar and colleagues proposed “familial cortical myoclonic tremor with epilepsy” as unifying term [1]. Four different autosomal dominant FCMTE loci have already been reported. FCMTE1 (8q23.3-q24.11) was identified in a large Japanese family who mainly presented with tremulous finger movement and/or myoclonus of the extremities at an average of age of 30.5 years. Previously, familial febrile convulsions and idiopathic generalized epilepsy syndrome were also mapped to chromosome 8q [2]. FCMTE2 (2p11.1-q12.2) was first described in a large pedigree from Tuscany who affected members presented with non-progressive cortical reflex myoclonus and generalized EEG abnormalities; however, in this family patients also had focal frontotemporal EEG abnormalities and some patients (n=3) additionally featured complex partial seizures. More Italian families were subsequently mapped to the same locus [4, 5], which was later refined in two European descent families by positional cloning techniques [6, 7]. FCMTE3 was first described in families from South Africa [8] but later mapped to chromosome 5p15.31-p15.1 in a large French family [3]. FCMTE4 (3q26.32-3q28) has recently been reported in a large family from Thailand, which consisted of 13 affected members and featured clinical symptoms similar to those previously reported [9].

Despite all genetic analyses performed in FCMTE families, no causal gene has been identified. In this context, whole exome sequencing (WES) is dramatically accelerating the field of biomedical research, particularly in Mendelian diseases, and is becoming a fruitful strategy for gene identification. Through the use of WES, novel genes have recently been identified in several neurological disease, including ET [10], and in families previously deemed statistically underpowered for positional cloning [11]. In this study we aimed to identify the genetic causes underlying FCMTE in a large Spanish family through the application of WES. As a result, a stop codon mutation (p.Trp26Stop) in the *ACMSD* gene, which is part of the kynurenine pathway, was identified as the disease-segregating mutation. ACMSD deficiency has already been implicated in the genesis of epileptic seizures [12] and

has been proved to result in quinolinate accumulation that is thought to be involved in various central nervous system phenomena, including synaptic plasticity and neurodegeneration [13].

We concluded that, while further studies are warranted to establish the molecular mechanisms by which *ACMSD* mutation may contribute to the development of cortical myoclonic tremor, epilepsy, and parkinsonism, both brain-specific kynurenic acid deficiency and quinolinate accumulation are likely to play an important role in the pathogenesis of cortical myoclonic tremor and epilepsy.

Materials and methods

Subjects

A detailed family pedigree was constructed by collecting clinical histories on all putatively affected as well as unaffected individuals and spouses. The inheritance pattern was autosomal dominant. There were 7 affected individuals over three different generations and full clinical evaluation was conducted in 4 affected individuals (Figure 1A, Table 1). Written informed consent, fully approved by the local ethics committee at the *Hospital Universitario Donostia*, was obtained from all participants. All members' DNA samples were isolated from whole blood using standard procedures.

94 DNA samples belonging to ethnicity-matched neurologically normal individuals (49 females and 45 males) and without family history of any movement disorders were also available. The age at sample collection of the control individuals ranged from 60 to 93 years with an average of 69.1 years.

11 familial and 58 sporadic cases featuring ET and 54 sporadic cases featuring late-onset Parkinson's disease (LOPD) were additionally available.

All cases examined were from the same geographical region in the North of Spain.

Neuropsychological and Electrophysiological Studies

The Montreal Cognitive Assessment (MoCA), which assesses different cognitive domains (http://www.mocatest.org/), was used for the determination of cognitive dysfunction.

Electroencephalographies (EEGs) were obtained after the application of electrodes and conducting jelly, using the International 10-20 System of Electrode Placement. Standard techniques for nerve conduction studies were used. Peroneal and tibial motor responses and sural sensory responses were recorded. For somatosensory evoked potentials (SEP), the median nerve at the wrist was stimulated and upper limb SEP were recorded at the contralateral scalp (C3′ and C4′: 2 cm posterior to C3 and C4 on the international 10-20 system). Stimulation rate was 3 Hz with duration of 0.2 msec. Digital averaging was performed using 200 samples; the filters were set at a high cut of 500 Hz and a low cut of 10 Hz. The latencies of the N20 and P25 peaks and the interpeak amplitudes of N20-P25 were analysed. Averaging was typically performed three times to ensure reproducibility.

Surface electromyographies (EMGs) were recorded from wrist extensor and flexor muscles using surface electrodes placed over the muscle bellies 3 cm apart. The filters were set with a bandpass of 10Hz-1kHz. A triaxial accelerometer was placed over the first dorsal interosseous muscle of the hand.

C-reflexes were recorded from the abductor pollicis brevis muscle after delivering a supramaximal stimulus over median nerve in the wrist.

WES

WES was performed in three affected cases (I-5, II-3, and III-1; Figure 1A). The SureSelect Human All exon 50Mb exon-capture kit was used for library enrichment (Agilent Technologies Inc., Santa Clara, CA, USA). The captured exome libraries were then sequenced on a HiSeq2000 according to the manufacturer's instructions for paired-end 100-bp reads (Illumina Inc, San Diego, CA, USA) and on a single flow cell lane each to capture the maximum possible genetic variation. After sequencing, data were put through a computational pipeline for WES data processing and analysis following the general workflow adopted by the 1000 genomes project and analyzed as previously described [14].

Later, any potential mutation observed as common variation in the dbSNP137 or 1000 Genomes Project Phase 1 was removed for further analyses. Genetic variants mapping to intra-genic, intronic, and non-coding exonic regions, with the exception of those variants mapping close to splice sites, were also removed since they are unlikely to be causative. Genetic variants present in other public databases, such as the Exome Variant Server of the National Heart, Lung, and Blood Institute (NHLBI) Exome Sequencing Project (http://evs.gs.washington.edu/EVS/) [15] and exomes generated in house were also removed.

To assist in causative gene identification, the pathogenicity of each disease-segregating mutation was predicted by two computational methods previously evaluated as most efficient [16] (Figure 1A, Table 2). The HomoloGene database from NCBI web site was also used to examine the conservation of both disease-segregating mutations in different species (http://www.ncbi.nlm.nih.gov/homologene).

Gene screening analyses

Genomic primers for PCR amplifications were designed using a primer design public website (http://ihg.gsf.de/ihg/ExonPrimer.html). Primers were used to amplify *ACMSD and MYBBP1A* all coding exons and splice sites (Electronic supplementary material). PCR amplifications and sequencing reactions were performed and analyzed as previously described [14].

Results

Here we report a family featuring a heterogeneous form of FCMTE. Clinical characteristics in affected members included seizures and postural hand tremor. Gait and postural disturbances that were levodopa responsiveness were also seen in one patient. Table 1 includes the main phenotypic characteristics of the four affected individuals fully examined by us (I-5, II-3, III-1, and III-7). More detailed clinical information about these four patients, three additional patients not examined by us (I-9, II-5, and II-8), and three neurologically unaffected family members, of which two (II-12 and II-13) have recently been examined by us, are described below. The clinical information of patients not examined by us was collected from medical records and communications with patients' relatives.

Patients' clinical details

Patient 1 (I-5)—At the age of 17 he started suffering from myoclonic and generalized seizures that were rare and precipitated by sleep deprivation or alcohol intake. At 20 years of age he also showed tremor of both hands. Seizures had good response to medications but his tremor worsened considerably after treatment with valproate. At the age of 63 epileptic seizures disappeared and the medication was discontinued. At the age of 73 he was cognitively normal and had no intolerance of light. He had postural tremor of both hands without any cerebellar, rigid-akinetic, or dystonic signs. EMG recorded in the arms showed 4-5Hz frequency with co-contraction of agonists and antagonists muscles. Brain MRI

showed mild temporoparietal atrophy (data not shown). He died in 2011 due to a right temporal lobe hematoma.

Patient 2 (I-9)—He suffered from epilepsy since childhood but no history of tremor was collected. He also had diabetes and a chronic lung disease and died at the age of 63 of lung squamous carcinoma.

Patient 3 (II-3)—This is a 53-yearl-old woman who suffered from postural tremor of both hands since the age of 17 and generalized convulsive seizures since the age of 20. Treatment with sodium valproate (2000 mg/day) kept her in good seizure control but worsened her tremor. At the age of 49 she complained of a gait disorder. On examination, she showed hypomimia, mild gait and postural disturbance, orthostatic tremor, mild akinesia, and rigidity of neck and arms. A diagnosis of parkinsonism was made and treatment with carbidopalevodopa (300 mg/day) was given. The sodium valproate was later replaced by levetiracetam (2000 mg/day) and she developed new seizures without improvement of parkinsonism. On her last neurological examination, she had high intolerance of light and wore sunglasses to avoid photosensitive myoclonic seizures. She had rhythmic involuntary movements in her upper and lower extremities particularly induced by posture and action. The tremor of her hand became more severe with a postural component and her leg tremor worsened during orthostatism, increasing her postural instability. Her gait was slow with short steps and hesitations during turns. Reflexes were brisk and plantar responses were flexor. Ocular movements and finger-nose-finger and heel-shin coordination tests were normal. She showed mild deficits in attention, memory, and executive function (MoCA score 19/30). Her EEG showed generalized spike and wave complexes more predominant in the left frontotemporal area. SEP were giant with amplitude of 15μV in both sides. Bilateral C-reflexes were obtained in abductor pollicis brevis. Surface EMG showed a myoclonic tremor with irregular bursts of agonist and antagonist muscle co-contraction at a frequency of 4-6Hz, which confirmed that the tremor was actually myoclonus, and showed periodic, irregular muscle bursts with short burst duration of about 50ms. Brain MRI showed mild cerebellar atrophy and high-intensity signals in T2 and Flair- weighted images in ventral area of brainstem, and a bilateral linear hypointense images in Inversion Recovery (IR) sequences, suggesting a corticospinal tract wallerian degeneration (Figure 1D).

Patient 4 (II-5)—This is a 55-year-old woman who presented with seizures in her teens and is now without treatment.

Patient 5 (II-8)—This is a 54-year-old man who suffers from seizures and is now on treatment.

Patient 6 (III-1)—This 28-year-old man had myoclonic and generalized seizures, properly controlled with sodium valproate (1000 mg/day), since the age of 17. He had mild hand tremor but showed no signs of photosensitivity or gait disturbances. He was cognitively normal (MoCA: 30/30). His neuropsychological evaluation showed normal EEG without photoparoxismal response. SEP had a normal amplitude (6μV). C-waves were no obtained and surface EMG revealed an irregular tremor at 8-10 Hz with co-contraction of agonist and antagonist muscles of the forearm. His brain MRI was also normal.

Patient 7 (III-7)—This is a 23-year-old man. Starting from age 22, he had several partial secondarily generalized convulsive seizures that are properly controlled with oxcarbazepine (1200 mg/day) and clonazepam (1mg/day). He has mild hand tremor that sometimes exacerbates without disabling him and feels some photosensitivity. He had a MoCA score of 30/30 and normal brain MRI. His EEG and SEP (2μV) were normal. C-waves were no

obtained and surface EMG revealed an irregular tremor at 8-10 Hz with co-contraction of agonist and antagonist muscles of the forearm.

Brief medical records for three additional family members were also available. For individual II-11 no history of tremor or epilepsy was recorded. Individual II-12 was reported to have gait disturbances and personality problems with intellectual disability but not tremor or epilepsy. Currently, she is not taking any medication and her last neurological examination revealed mild ataxia with areflexia in the legs and progressive distal sensory loss. She had a MoCA score of 25 and normal EEG. Individual II-13 had one or two episodes of loss of consciousness at the age of 10 but at 45 years old she is neurologically normal with a MoCA score of 30/30 and normal EEG.

WES

More than 85% of the target exome was captured at 20-fold coverage or higher: 85.68% for patient I-5, 85.36% for patient II-3, and 89.15% for patient III-1. After an adequate filtering of common genetic variation, 181 non-synonymous and 7 nonsense SNVs were identified for patient I-5, 209 non-synonymous and 7 nonsense SNVs for patient II-3, and 241 non-synonymous and 6 nonsense SNVs for patient III-1. Of these only two, highly conserved among other species and absent in large number of control individuals (n>10,000), including 188 ethnicity-matched control chromosomes, were identified as disease-segreagting mutations (Figure 1A). These variants were both a G to A transition resulting in p.Trp26Stop and p.Ala920Thr, respectively. Only the p.Trp26Stop mutation, which lies in the *ACMSD* gene (MIM #608889) that encodes for the α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase, was predicted to be pathogenic (Table 2). ACMSD is an enzyme that is part of the kynurenine pathway of tryptophan degradation in mamals and reacts with α-amino-β-carboxymuconate-ε-semialdehyde (ACMS) to produce α-aminomuconate-ε-semialdehyde (AMS). Under absence of ACMSD, ACMS is unstable and rapidly converts to quinolinate (quinolinic acid; QA), which is a potent excitotoxin thought to be involved in the pathogenesis of neurodegenerative diseases such as epilepsy, Alzheimer's disease, and Huntington's disease [17-20]. The p.Ala920Thr mutation is located in the *MYBBP1A* gene (MIM #604885); *MYBBP1A* encodes for MYB binding protein (P160) 1A, which acts as tumor suppressor and is essential for early embryonic development, controls cell cycle, and mitosis [21].

Based on the evidence that the kynurenine pathway has already been involved in the genesis of epileptic seizures [22] and alterations in the levels of the kynurenine pathway metabolites have been implicated in several neurological conditions, including Hungtington disease, Alzheimer disease, and Parkinson's disease [23], we concluded that the ACMSD mutation identified here is likely to be pathogenic and responsible for the cortical myoclonic tremor and epilepsy seen in our patients.

Later, due to the proximity of *ACMSD* to FCMTE2, the entire coding region and splice sites of *ACMSD* were examined in two families previously linked to this locus. Because tremor of both hands is a common feature of all our patients, these were also examined in 11 familial and 58 sporadic cases featuring ET. Sequencing data of 3′ and 5′ *ACMSD* untranslated regions were also available and investigated in the 11 familial cases. And since genetic variants close to the *ACMSD* locus were previously associated with an increased risk for sporadic PD [24], the p.Trp26Stop mutation was also examined in 54 sporadic LOPD patients by direct Sanger sequencing. No additional mutation carrier was identified.

Discussion

We here report a large family featuring a heterogeneous form of FCMTE. All patients suffered from cortical myoclonic tremor, which could be misdiagnosed of ET in the first stages of the disease, and epilepsy. In one individual the epilepsy disappeared in the adulthood. As the family described by Magnin and colleagues [25], one of our patient (II-3) also had gait disturbances, cognitive impairment, and photosensitivity that appeared during the disease progression and under treatment with valproate. The anomaly seen in the brain MRI of this patient (Figure 1D) that may explain her variable phenotype has never been described in previously reported FCMTE families [26]. This patient was first diagnosed of L-dopa responsive parkinsonism, however the semiology of the gait disturbance, the type of tremor, and the remaining motor symptoms differ from the phenotype described in PD. For instance, her instability associated with the orthostatic tremor of the lower extremities has never seen in PD. Another, relatively young patient (III-7) also felt some light sensitivity that might enhance with the disease progression. Although the mother (II-11) of this patient was not available for examination, given the AD pattern of inheritance of this family, she is an obligate carrier. Two of her sisters were also examined, however none them developed epilepsy or tremor (Figure 1A).

In order to identify the genetic causes underlying disease in our family, WES was performed in three affected individuals of three different generations. This led us to identify two disease-segregating mutations in *ACMSD* and *MYBBP1A* genes, respectively (Table 2). Both mutations (Trp26Stop and p.Ala920Thr) were absent in large number of control chromosomes, including ethnicity matched controls, but only the mutation in *ACMSD*, p.Trp26Stop, which causes a premature stop codon and is conserved among other orthologs, was predicted to be pathogenic (Figure 1B/C). The fact that only one family was identified with mutations in this gene is not surprising, as almost each FCMTE family maps to a different locus. The absence of pathogenic mutations in two families previously linked to FCMTE2 also suggests that *ACMSD* is not responsible for the FCMTE2 phenotype and the FCMTE2 gene remains to be discovered. While it is also possible that the *ACMSD* disease-segregating mutation that causes a truncated protein may be a very rare benign variant, the already-known involvement of kynurenines in the genesis of epileptic seizures in mice, frogs, and rats further supports its pathogenicity [20]. Even though we were unable to identify any ET or LOPD patient with mutations in *ACMSD*, the presence of tremor in all our patients and the observation of parkinsonism in one of them support the possibility that the nigrostriatal dopaminergic system may also be vulnerable to *ACMSD* mutation, as suggested by previously published GWAS studies [24]. However this should be interpreted with caution since only one of our patients presents with parkinsonism, the PD-associated SNPs lie outside the *ACMSD* locus, and this association, which showed moderate evidence of heterogeneity across populations [24], has not been replicated by all PD-associated GWAS studies [27].

The association of *ACMSD* mutation with cortical myoclonus, epilepsy, and parkinsonism is very interesting. Human ACMSD, predicted to be a cytosolic enzyme, is expressed at very low but significant levels in the brain [28]. ACMSD is part of the kynurenine pathway, which is the main route of tryptophan metabolism. Many kynurenines, including quinolinate, which levels increase at ACMSD deficiency, cannot cross the blood-brain barrier, or do very poorly, and as such must be formed locally within the brain [12], suggesting that the regulation of quinolinate is brain-specific. While we were unable to examine the brain-specific ACMSD in our patients, the ACMSD expression levels have already been shown to be highly correlated to the enzyme activity levels [28], suggesting that the *ACMSD* mutation identified in our patients probably results in a significant decrease of its enzymatic activity. It has additionally been shown that the inhibition of ACMSD

blocks the conversion of tryptophan to picolinic acid (PA), which results in cellular QA accumulation (Figure 2) [29], and that intracerebroventricular inyection of QA causes seizure activity in mice [18]. Taken together, we hypothesize that the *ACMSD* p.Trp26Stop mutation may result in a significant increased of the cellular QA levels in the brain, probably due to impairments in its enzymatic activity, leading to the initiation and propagation of seizures. These QA-induced seizures have been shown to be associated with increased levels of extracellular KYNA, suggesting that high KYNA levels arise as a response to the seizure activity and are therefore neuroprotectives [20, 30].

In addition, the involvement of abnormal serotonin transmission in the generation of seizures and myoclonus has been discussed for a long time. In particular, previous research has demonstrated a reduction of tryptophan and other serotonin metabolites in animals and patients with PME as well as cerebrospinal fluid of patients with cortical myoclonus; recent data also support the implication of altered tryptophan metabolism in the pathogenesis of Unverricht-Lundborg disease [31, 32]; and both 5-hydroxy-L-tryptophan and alpha-lactoalbumin have already been used for the treatment of myoclonus [33, 34].

In conclusion, despite that further studies are warranted to elucidate the molecular mechanisms by which *ACMSD* mutation may cause cortical myoclonus, epilepsy, and parkinsonism, we conclude that the disease-segregating *ACMSD* p.Trp26Stop mutation is likely to be responsible for the FCMTE phenotype seen in our patients. This finding supports the evidence that cellular changes in the metabolites of the kynurenine pathway are implicated in neurodegeneration [12, 23] and suggests that both brain-specific KYNA deficiency and QA accumulation may also be important factors in the pathogenesis of cortical myoclonic tremor and epilepsy. Ultimately, the kynurenine pathway is likely to be a potential drug target for treating these and other devastating neurodegenerative disorders [35].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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KEY MESSAGES: JMME-D-13-00147R1

- ACMSD is mutated in a family with cortical myoclonus, epilepsy, and parkinsonism.
- ACMSD mutation contributes to the development of FCMTE.
- QA accumulation is likely to play an important role in the pathogenesis of FCMTE.
- The kynurenine pathway as a potential drug target for the treatment of epilepsy.

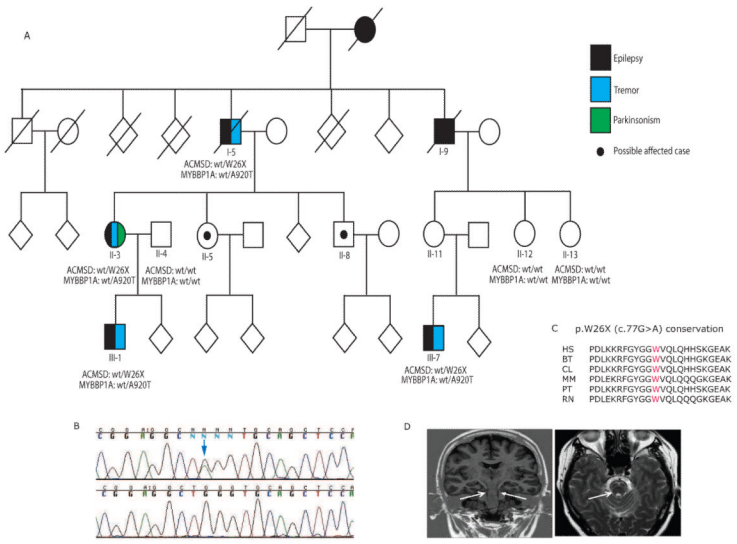

Figure 1.

A) Pedigree structure of the Spanish family featuring a complex form of FCMTE. Both disease-segregating mutations are shown. B) Sequence chromatograms showing the *ACMSD* wild-type mutation sequence at the bottom and the heterozygous *ACMSD* mutant sequence at the top (Blue arrow). C) *ACMSD* p.W26X mutation conservation across different species is represented. HS: homo sapiens; BT: Bos Taurus; CL: Canis Lupus; MM: Mus musculus; PT: Pan troglodytes, RN: Rattus Norvegicus. D) Brain MRI of patient II-3. Left: Coronal Inversion Recovery (IR): hypointense linear signals (arrows) in the corticospinal pathways. Right: Transversal T2 weighted image showing a high-intensity signals in the brainstem (arrow). Mild vermian cerebellar atrophy is shown.

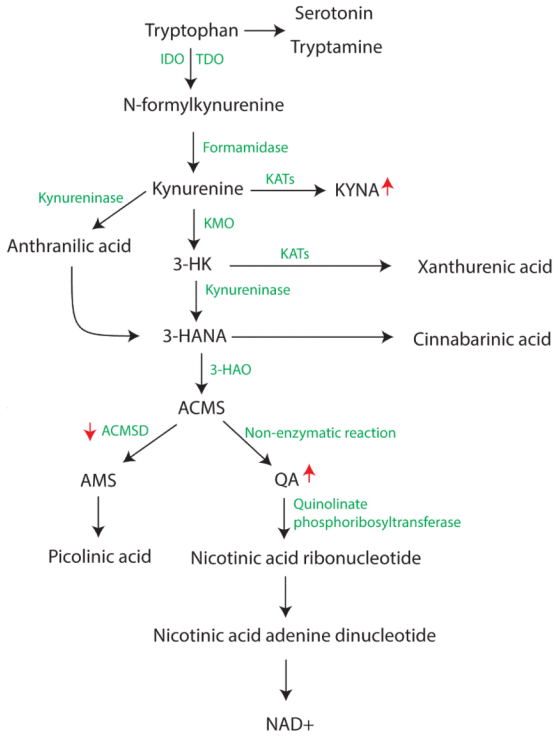

Figure 2.

Diagram of the kynurenine pathway of tryptophan degradation in mammals [12, 35]. In red is highlighted what is believed to occur in the presence of ACMSD deficiency. KYNA levels are elevated in response to seizure activity. IDO: Indoleamine 2,3-dioxigenase; TDO: Tryptophan 2,3-dioxygenase; KYNA: Kynurenic acid; KATs: Kynurenine aminotransferases; 3-HK: 3-hydroxykynurenine; 3-HANA: 3-hydroxyyanthranilic acid; 3-HAO: 3-hydroxyyanthranilic acid 3,4-dioxygenase; ACMSD: α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase; ACMS: α-amino-β-carboxymuconate-ε-semialdehyde; AMS: α-aminomuconate-ε-semialdehyde; QA: Quinolinic acid (quinolinate).

Table 1

Clinical and neurophysiological findings in patients with benign adult familial cortical myoclonic epilepsy

Patient ID	Gender	Age at follow-up	Age at onset of tremor	Age at onset of GTC	EEG	Photic	Giant SEP	Medication	Seizures frequency (Past year)
I-5	M	73	20	17	Multifocal PSW	−	N/A	PB, VPA, none	None
II-3	F	52	17	20	Focal PSW	+	15μV (Both sides)	VPA, LVT, L-Dopa	5 (Yearly)
III-1	M	28	N/A	17	Normal	−	−	VPA	None
III-7	M	23	23	22	Normal	Mild	−	OXCBZ, CZP	3 partials

EEG: Electroencephalogram, GTC: Generalized tonicclonic convulsions, SEP: Somatosensory evoked potentials, PSW: Polyspikes and waves, PB: Phenobarbital, VPA: Valproic acid, LVT: Levetiracetam, OXCBZ: Oxcarbazepine, CZP: Clonazepam, N/A: Not available, −: Absence, +: Present.

Table 2

Disease-segregating mutations identified through WES and subsequent analyses in a Spanish family featuring FCMTE

Gene	Chr	Nucleotide variation	Protein variation	Spanish Control Population (n=188)	Pathogenecity Prediction (MutPred/SNPs&Go)	Expression	Associated disease
ACMSD	**2q21.3**	**c.77G>A**	**p.W26X**	**Absent**	**Truncated protein**	**Kidney, liver, and brain**	**Epilepsy, Alzheimer and Huntington**
MYBBP1A	17p13.3	c.2758G>A	p.A920T	Absent	0.592/Neutral	Highly expressed	Tumor suppressor

Highlighted in bold is the disease-segregating mutation responsible for the FCMTE phenotype seen in our patients.Computational methods for pathogenecity prediction: MutPred (http://mutpred.mutdb.org/) and SNPs&GO (http://snps-and-go.biocomp.unibo.it/snps-and-go/).