**EFHC1:** A gene for juvenile myoclonic epilepsy

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**Summary**

We originally reported mutations of *EFHC1* gene in patients with juvenile myoclonic epilepsy (JME). Subsequently, several other groups reported additional *EFHC1* mutations in patients with JME and also in other types of idiopathic generalized epilepsy. We recently generated Efhc1-deficient mouse and found that the mouse showed spontaneous myoclonus and increased susceptibility to a convulsant, pentylenetetrazol. These results further support and confirm our proposal that *EFHC1* is the gene for JME.

**Introduction**

Juvenile myoclonic epilepsy (JME) is characterized by adolescent onset myoclonic jerks on awakening; grand mal clonic; tonic clonic and tonic clonic seizures; and less frequent absence seizures. JME is one of the most common epilepsies, accounting for 3% to 12% of all known epilepsies [1]. Electroencephalography reveals 15-30 Hz multispikes during myoclonic and tonic clonic convulsions. Using genetic linkage analyses on Mexican JME families, we previously mapped and narrowed one of the chromosomal loci harboring genes...
responsible for JME down to chromosome 6p12 [2]. After extensive gene searches [3, 4, 5], we finally identified the gene for JME on 6p12, which we named \(\text{EFHC1} \) (EF hand domain containing 1) [6]. The human \(\text{EFHC1}\) encodes a 640 amino acid non-ion channel protein "myoclonin 1" that harbors three tandemly repeated DM10 domains, a motif of unknown function, and one EF-hand calcium-binding motif at the carboxyl terminus. \(\text{EFHC1}\) mRNA was detected in multiple tissues including the brain in Northern blot analyses [6]. Ikeda and colleagues [7] reported that mouse myoclonin 1 is expressed in tracheal cilia and sperm flagella. We also reported that mouse myoclonin 1 protein is dominantly expressed in prenatal choroid plexus, and in the cilia of ependymal cells lining the wall of ventricles in postnatal stages [8].

Successive mutation studies by other groups reported \(\text{EFHC1}\) heterozygous missense mutations in a Caucasian family [9] and Italian families [10] with JME. In addition to the mutations in JME, Stogmann and colleagues [11] described \(\text{EFHC1}\) mutations in other types of idiopathic epilepsies comprising juvenile absence epilepsy, cryptogenic temporal lobe epilepsy, and an unclassified idiopathic epilepsy. Furthermore, we recently reported additional \(\text{EFHC1}\) missense mutations as full-length and truncated mutations in a short isoform of \(\text{EFHC1}\) in Mexican and Japanese patients [12]. In addition to the original full length myoclonin 1, the \(\text{EFHC1}\) gene also encodes a short isoform of myoclonin 1 (278 amino acids) that harbors only one DM10 domain without an EF hand motif, and a unique carboxyl-terminal end [4]. We identified heterozygous frameshift and nonsense mutations in the portion of \(\text{EFHC1}\) transcript encoding the unique carboxyl-terminal end of the myoclonin 1 short isoform in 3 JME families (2 families from Honduras and one from Mexico) [12].

To further address the putative relevance of \(\text{EFHC1}\) in epilepsies, we generated and characterized the \(\text{Efhc1}\) deficient mice [13]. Most of the mice are normal in outward appearance and both sexes are fertile. However, the ventricles of the brains are significantly enlarged in the null mutants but not in the heterozygotes. Although the ciliary structure is normal, the ciliary beating frequency is significantly reduced in null mutants. In adult stages, both the heterozygous and null mutants develop frequent spontaneous myoclonus. Furthermore, the threshold of seizures induced by pentylenetetrazol is significantly reduced in both heterozygous and null mutants [13].

All the above mentioned results support our contention that \(\text{EFHC1}\) is a gene responsible for epilepsies; however the molecular pathological cascade is still largely unknown. Recently, de Nijs and colleagues [14] reported that myoclonin1 interacts with microtubules, and regulates cell division and cortical development. In their study, the suppression of \(\text{Efhc1}\) via \textit{ex vivo} electroporation of shRNA in rat brain induced abnormal (suppressed) radial migration of neurons, cell division, and cell cycle exit. However, these features are too drastic when compared to those of our \(\text{Efhc1}\) deficient mice [13], and their results may have
to be confirmed by conducting additional experiments. Anyway, their study [14] as well as our study [13] still have not directly answered the question "How EFHC1 mutations cause epilepsies?", and further studies are definitely required to fully understand the pathological cascade.

References


Mutational analysis of EFHC1 gene in Italian families with juvenile myoclonic epilepsy. Epilepsia 2007; 48: 1686-1690.


