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ABOUT COVER

Editorial Board Member of *World Journal of Psychiatry*, Massimo Pasquini, MD, PhD, Associate Professor, Doctor, Department of Human Neurosciences, Sapienza University, Rome 00185, Italy. massimo.pasquini@uniroma1.it

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Molecular typing of familial temporal lobe epilepsy

Chao Liu, Xiao-Zhi Qiao, Zi-Han Wei, Mi Cao, Zhen-Yu Wu, Yan-Chun Deng

ORCID number: Chao Liu 0000-0002-8154-918X; Xiao-Zhi Qiao 0000-0001-9604-4929; Zi-Han Wei 0000-0003-0299-5163; Mi Cao 0000-0002-9307-939X; Zhen-Yu Wu 0000-0003-2118-7372; Yan-Chun Deng 0000-0002-1281-8999.

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Chao Liu, Xiao-Zhi Qiao, Zi-Han Wei, Mi Cao, Yan-Chun Deng, Department of Neurology, The First Affiliated Hospital of Air Force Medical University, Xi'an 710032, Shaanxi Province, China

Zhen-Yu Wu, Department of Anatomy, Histology and Embryology and K.K. Leung Brain Research Centre, School of Basic Medicine, Air Force Medical University, Xi'an 710032, Shaanxi Province, China

Corresponding author: Yan-Chun Deng, MD, PhD, Chief Doctor, Professor, Department of Neurology, The First Affiliated Hospital of Air Force Medical University, No. 127 Changle West Road, Xi'an 710032, Shaanxi Province, China. yanchund@fmmu.edu.cn

Abstract

The pathogenesis of temporal lobe epilepsy (TLE) was originally considered to be acquired. However, some reports showed that TLE was clustered in some families, indicating a genetic etiology. With the popularity of genetic testing technology, eleven different types of familial TLE (FTLE), including ETL1-ETL11, have been reported, of which ETL9-ETL11 had not yet been included in the OMIM database. These types of FTLE were caused by different genes/Loci and had distinct characteristics. ETL1, ETL7 and ETL10 were characterized by auditory, visual and aphasia seizures, leading to the diagnosis of familial lateral TLE. ETL2, ETL3 and ETL6 showed prominent autonomic symptom and automatism with or without hippocampal abnormalities, indicating a mesial temporal origin. Febrile seizures were common in FTLEs such as ETL2, ETL5, ETL6 and ETL11. ETL4 was diagnosed as occipitotemporal lobe epilepsy with a high incidence of migraine and visual aura. Considering the diversity and complexity of the symptoms of TLE, neurologists enquiring about the family history of epilepsy should ask whether the relatives of the proband had experienced unnoticeable seizures and whether there is a family history of other neurological diseases carefully. Most FTLE patients had a good prognosis with or without anti-seizure medication treatment, with the exception of patients with heterozygous mutations of the *CPA6* gene. The pathogenic mechanism was diverse among these genes and spans disturbances of neuron development, differentiation and synaptic signaling. In this article, we describe the research progress on eleven different types of FTLE. The precise molecular typing of FTLE would facilitate the diagnosis and treatment of FTLE and genetic counseling for this disorder.

Key Words: Temporal lobe epilepsy; Gene mutation; Gene locus; Phenotypes; Prognosis

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Core Tip: Eleven types of familial temporal lobe epilepsy (FTLE) caused by single gene mutations or specific gene loci had been identified to date. The phenotype of FTLE was heterogenous and includes typical temporal lobe seizures and specific symptoms. We herein describe the etiology, inheritance, phenotype and prognosis of each type of FTLE and summarize their similarities and differences.

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INTRODUCTION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate two unprovoked seizures > 24 h apart[1]. Epilepsy could be classified as focal, generalized, combined generalized and focal, and unknown according to the origin of the seizures[2]. Epilepsy affected approximately 50 million people worldwide, among which up to 60%-70% of affected individuals had focal epilepsy[3, 4]. Epilepsy and its comorbidities, such as memory and psychiatric disorders, severely lower the quality of life of patients[5]. Temporal lobe epilepsy (TLE), including mesial TLE (MTLE) and lateral TLE (LTLE), was the most common type of focal epilepsy, especially in adults[6]. The causes of TLE were heterogeneous, and the overall prognosis of TLE was far from satisfactory[7].

The first description of an instance of familial TLE (FTLE) could be traced back to 1895, before TLE had been defined[8,9]. In 1994, Berkovic *et al*[10] provided the first report of familial TLE, in which four individuals in two generations were diagnosed with TLE. The family aggregation of TLE indicated a genetic etiology. Although the characteristics of TLE had been extensively studied, the genetic etiology of TLE remains unclear, and the incidence of FTLE were severely underestimated due to the high rates of misdiagnosis and missed diagnosis in individuals with subtle symptoms [11]. Leucine-rich glioma inactivated-1 (*LG11*) mutations was identified in approximately 50% of families with LTLE and 3% of sporadic LTLE cases[12,13]. Those findings had led to the hypothesis that LTLE was commonly caused by gene mutations and promoted the exploration of the genetic causes of LTLE[14]. Seventy percent of MTLE cases were considered to be caused by hippocampal sclerosis (HS) and was drug-refractory[15]. Most patients with drug-refractory MTLE had to undergo costly surgery, although 30% of such patients experience relapse within two years[16]. Many reports had shown that HS and MTLE were inheritable[17,18]. The mechanism seemed polygenic and was affected by multiple factors[19]. Further exploration of the underlying pathogenic genes and molecular mechanisms was critical for precision medicine.

Eleven genes/Loci responsible for FTLE have been reported to date (Table 1), including the genes *LG11*, carboxypeptidase A6 (*CPA6*), reelin (*RELN*), galanin and GMAP prepropeptide (*GAL*), DEP domain containing 5 (*DEPDC5*), microtubule associated monoxygenase, calponin and LIM domain containing 1 (*MICAL-1*) and sodium voltage-gated channel alpha subunit 1 (*SCN1A*), along with gene loci on chromosomes (Chr) 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26. These genes were involved in different biological processes. In this article, we describe the research progress on eleven types of FTLE, ETL1-ETL11, caused by these genes/Loci, of which ETL9-ETL11 had not yet been recorded in the OMIM database.

ETL1, RELATED TO LG11 GENE MUTATION

ETL1 (OMIM 600512) was first reported by Ottman *et al*[20] in a family in which 11 members in three generations had seizures, with most seizures having auditory features, suggesting a neocortical (or lateral) temporal lobe origin. Linkage analysis

Table 1 Eleven different types of familial temporal lobe epilepsy

Phenotype	OMIM ID	Gene/locus	Inheritance	Age at seizure onset (yr)	Seizure types	EEG	MRI	Epilepsy types	Prognosis	Ref.
ETL1	600512	LG11	AD	4-50	Aud, Aph, FBTCs	T ea	Nor	LTLE	Responsive to ASM	[20,24,25]
ETL2	608096	Chr12q22-q23.3	AD	0.75-35	FS, FBTCs; Cog, Aut	Nor, T ea	HM	MTLE	Responsive to ASM or SR	[27,28]
ETL3	611630	Chr4q13.2-q21.3	AD	5-18	Cog, FBTCs, FIAS	Nor, T ea	Nor	MTLE	Responsive to ASM or SR	[32]
ETL4	611631	Chr9q21-q22	AD	0.58-63	Focal Mot; Cog, Sen, Aut, FIAS, FBTCs	Nor	Nor	OTLE	Responsive to ASM or SR; migraine 5/Mo - 2/y	[33]
ETL5	614417	CPA6	AR	0.75-5	FS, FBECTS, FIAS	T ea	T atr, HS	TLE	Responsive to ASM or SR	[36]
			AD	1.25-23	FS	-	T atr	TLE	Drug-refractory	[36]
ETL6	615697	Chr3q25-q26	AD	3-46	FS, FIAS, Cog, Sen, Aut, FBTCs	Nor, T ea, sa	Nor	MTLE	Responsive to ASMs	[37]
ETL7	616436	RELN	AD	8-40	Vis, Aud, FBECTS, FIAS	T ea	Nor	LTLE	Responsive to ASM or SR	[38,40]
ETL8	616461	GAL	AD	13	FIAS, Cog, Sen, Aut, FBTCs	T ea	Nor	TLE	Responsive to ASM	[43]
ETL9	-	DEPDC5	AD	8-13	FS, Cog, Sen, focal Mot; FBECTS	T ea	Nor	TLE	Responsive to ASM	[44,46,47]
ETL10	-	MICAL-1	AD	6-30	Aud, Aph, FBECTS	T or FT ea	Nor	LTLE	Responsive to ASM	[48]
ETL11	-	SCN1A	AD	10-13	FS, FIAS, Aut; focal Mot, FBECTS	T ea	HS	TLE	Responsive to ASM	[50]

AD: Autosomal dominant; Aph: Aphasia; AR: Autosomal recessive; ASMs: Anti-seizure medications; atr: Atrophy; Aud: Auditory; Aut: Autonomic; Chr: Chromosome; CPA6: Carboxypeptidase A6; Cog: Cognitive; DEPDC5: DEP domain containing 5; ea: Epileptic activity; EEG: Electroencephalogram; Emo: Emotional; ETL: Epilepsy, familial temporal lobe; FBTCs: Focal to bilateral tonic-clonic seizures; FIAS: Focal impaired awareness seizure; FS: Febrile seizures; FT: Frontotemporal; GAL: Galanin and GMAP prepropeptide; HM: Hippocampal malrotation; HS: Hippocampal sclerosis; LG11: Leucine-rich glioma inactivated-1; LTLE: Lateral TLE; MICAL-1: Microtubule associated monooxygenase, calponin and LIM domain containing 1; MTLE: Mesial TLE; Mot: Motor; MRI: Magnetic Resonance Imaging; Nor: Normal; OTLE: Occipitotemporal lobe Epilepsy; RELN: Reelin; sa: Slow activity; SCN1A: Sodium voltage-gated channel alpha subunit 1; Sen: Sensory; SR: Spontaneous remission; T: Temporal; TLE: Temporal lobe Epilepsy; Vis: Visual.

revealed that the candidate epilepsy gene was located on Chr 10q22-q24. In 2002, an *LG11* gene mutation on Chr 10q22-q24 was identified as the pathogenic cause[21]. *LG11* is a 60-kDa secreted protein that is predominantly expressed in neuronal cells in the brain and is involved in cortical neuronal migration, neuronal excitability and synaptic transmission. *LG11* mutations could lead to protein folding failure and destroy the interaction with its ligand, *ADAM22*[22].

More than 40 *LG11* variants related to ETL1 had been detected to date[23]. The variants were usually inherited from the affected parents and were rarely de novo, and the overall penetrance of the disorder was 61%-67%. The age of seizure onset was 4-50 years, usually 12-30 years[24]. Auditory and/or sensory aphasia seizures were the most common seizure types, and interictal electroencephalogram (EEG) showed temporal lobe origin, which supports the diagnosis of LTLE. The auditory symptoms ranged from unformed sounds, such as humming and ringing, to distortions and volume changes. Autonomic symptoms were less common. Most patients had experienced focal to bilateral tonic-clonic seizures (FBTCs). The prognosis was good with anti-seizure medications (ASMs), such as phenytoin and carbamazepine[25]. Some research has shown that treatment with the chemical corrector 4-phenylbutylate

ameliorates the increased seizure susceptibility of *LGII* mutant mice, which provides potential new therapeutic options for *LGII*-mediated epilepsy[26].

ETL2, RELATED TO THE 12Q22-Q23.3 LOCUS

Depondt *et al*[27] reported a 5-generation family in which 22 members had TLE and febrile seizures without HS. Claes *et al*[28] linked this phenotype, namely, ETL2 (OMIM 608096), to Chr 12q22-q23.3, which includes 280 genes. ETL2 was autosomal dominant inherited, and the penetrance was approximately 80%. Those patients had a high incidence of febrile seizures, and all febrile seizures disappeared before 6 years of age. The mean age at onset of afebrile seizures was 8 years. The most common seizure types included focal seizures with or without impaired awareness, such as sensation in the head, fear, confusion and viscerosensory and tonic-clonic seizures. Ten of the patients were diagnosed with MTLE. Hippocampal malrotation was common in this family, even in individuals without seizures. The prognosis was good, with 11 individuals experiencing spontaneous remission. In addition, there was a report of a family in which seven members had febrile seizures that evolved to tonic-clonic seizures. The genetic linkage analysis mapped to Chr 12q22-q23.3[29]. Recently, Maria *et al*[30] reported a sporadic case with TLE and febrile seizures who had a 12 Mb duplication at Chr12q22-q23.3. She presented with growth retardation. Her seizure was well controlled with carbamazepine. These findings indicated that Chr 12q22-q23.3 had a broad phenotypic spectrum, similar to most well-known epileptogenic genes[31]. The symptoms of patients from the same family showed high similarity, which might be related to the common mutation sites and genetic backgrounds. The exact pathogenic mechanism required further research.

ETL3, RELATED TO THE 4Q13.2-Q21.3 LOCUS

Hedera *et al*[32] reported a 4-generation family in which 11 individuals were diagnosed with MTLE or ETL3 (OMIM 611630). Linkage analysis mapped the phenotype to Chr 4q13.2-q21.3, which include 359 genes without homology to the well-known epileptic genes. ETL3 showed autosomal dominant inheritance with incomplete penetrance. The age of seizure onset was 5-18 years and most patients were 10-20 years. Ten individuals had focal cognitive seizures with feelings of déjà vu associated with dizziness or nausea, and 8 also had focal seizures with altered awareness and staring. Four individuals had FBCTS. Brain magnetic resonance imaging (MRI) was performed on 3 patients and the findings were not significant. EEG was performed on 6 patients, of whom 5 patients exhibited normal EEG and 1 had left anterior temporal sharp waves. Only 4 patients were treated with ASMs.

ETL4, RELATED TO THE 9Q21-Q22 LOCUS

ETL4 (OMIM 611631) was reported in a 5-generation family of which 14 individuals had occipitotemporal lobe epilepsy and migraine with visual aura[33]. Genome-wide linkage and haplotype analysis mapped the phenotype to Chr 9q21-q22, which include 604 genes. ETL4 was autosomal dominant and was inherited with a low penetrance of 75%. The age at seizure onset ranged from 7 mo to 63 years, and the median age was 21 years. Age at migraine onset ranged from 30 to 65 years, with a median age of 42 years. Ten individuals had occipitotemporal lobe epilepsy and 5 of them also had migraine with aura. Nine of the 10 patients had focal motor or nonmotor seizures, such as visual, autonomic, and somatosensory symptoms, olfactory and auditory hallucinations, and cognitive seizures excluding déjà vu. Three of the 10 patients had focal seizures with altered awareness and 3 had FBCTS. Four had a single isolated seizure, and 1 of them also had migraine with aura. Seizures and migraine attacks were temporally independent in all patients except one. EEG and brain MRI were normal except in 2 patients with age-related white matter changes.

Approximately 6% of migraine patients have seizures, and 8%-15% of epilepsy patients have migraines[34]. Tikka-Kleemola *et al*[35] reported that among 33 families of patients experiencing migraine with visual aura, 22 families were linked to Chr 9q21-q22. None of these family members had seizures. These findings indicated that epilepsy and migraine have a common genetic basis and that Chr 9q21-q22 was closely

related to epilepsy and migraine.

ETL5, RELATED TO CPA6 GENE MUTATION

Salzmann *et al*[36] reported four children with recessive familial forms of febrile seizures and TLE born to healthy first-cousin parents. A *CPA6* gene homozygous mutation was found associated with the phenotype and was named ETL5 (OMIM 614417). All 4 patients had febrile seizure onset before 4 years of age. One of them had TLE. His MRI showed right temporal atrophy, and EEG showed right temporal spikes and waves. They all became seizure-free with or without ASMs. In vitro research showed that *CPA6* variants reduced the level of protein expression and secretion and/or destroyed carboxypeptidase activity. Salzmann *et al*[36] also reported a sporadic case with drug-refractory TLE carrying compound heterozygous mutations in the *CPA6* gene. MRI showed cavernous malformation. His grandfather had a history of febrile seizures. Four unrelated patients with febrile seizures and refractory TLE carrying *CPA6* gene heterozygous mutations were also reported, suggesting that ETL5 was both recessively and dominantly inherited[36]. The seizure onset of these 4 patients ranged from 15 mo to 23 years of age. Among them, one had febrile seizures and left temporal lobe origin seizures with HS. His brother had a history of febrile seizures. Two patients had temporal lobe seizures originating from the temporo-parietal junction and bitemporal lobes. These two patients had neonatal sequelae and bitemporal atrophy on MRI. The last patient had febrile seizures, and his mother also had a history of febrile seizures. The prognosis of patients with homozygous mutations seemed to be better than that of patients with heterozygous mutations.

ETL6, RELATED TO THE 3Q25-Q26 LOCUS

Only one ETL6 (OMIM 615697) family had been reported to date by Chahine *et al*[37] in 2013. In the 4-generation family surveyed in the study, 7 individuals had TLE, and 4 had febrile seizures during childhood but no subsequent epilepsy. Genetic linkage analysis linked the phenotype to Chr 3q25-q26 containing 453 genes. ETL6 was autosomal dominant and inherited with incomplete penetrance. The age of onset of temporal seizures ranged from 3 to 46 years. The 4 patients with isolated febrile seizures had onset between 5 mo to 5 years of age. Seizure types included focal aware seizures, focal impaired awareness seizures, FBCTS and rarely status epilepticus. Many of the seizures were suggestive of a mesial temporal origin, and occurred with auras including abdominal discomfort, rising numbness, floating sensation, strange grabbing feeling, déjà vu and dizziness. Brain MRI, performed in 3 patients, was normal. EEG was normal except in 1 patient who exhibited sharp right temporal waves and irregular slow activity. The seizures of the patients were responsive to ASMs.

ETL7, RELATED TO RELN GENE MUTATION

Dazzo *et al*[38] identified seven different heterozygous missense mutations in the *RELN* gene in 7 unrelated families with LTLE or ETL7 (OMIM 616436). The *RELN* gene is crucial for the correct cytoarchitecture of laminated structures during embryonic development and modulates dendritic growth and synaptic plasticity in the postnatal and adult stages[39]. Their research revealed that the expression of reelin was reduced in the hippocampus of ETL7 patients and reelin promoter methylation was greater with severe granule cell dispersion, which supports a compromised reelin signaling pathway and identifies promoter methylation as an epigenetic mechanism in the pathogenesis of ETL7[38]. The clinical features of ETL7 were found to be similar to those of ETL1[40]. The mean age at seizure onset was 20 years. Seizure types included focal visual seizures, auditory seizures, déjà vu, FBCTS and focal seizures with impairment of consciousness. These patients were seizure-free with or without ASMs treatment. Previous work revealed that homozygous *RELN* gene mutations caused lissencephaly with cerebellar hypoplasia[41]. Three small consanguineous LCH-affected families had been reported thus far. The heterozygous individuals in these families exhibited reduced levels of reelin in their sera and were reported to be clinically normal[42]. The apparent normal phenotype of these individuals was

consistent with the low penetrance of *RELN* mutations.

ETL8, RELATED TO GAL GENE MUTATION

ETL8 (OMIM 616461) was reported by Guipponi *et al*[43] in a pair of monozygotic twin brothers with TLE carrying a heterozygous missense mutation in the *GAL* gene. The *GAL* gene encodes galanin, which is a neuropeptide highly expressed in the central nervous system. The mutant galanin identified in their study led to antagonistic activity against GALR1-mediated responses, decreased binding affinity and reduced agonist properties for GALR2 in vitro, suggesting that the variants impaired galanin signaling in the hippocampus and led to increased glutamatergic excitation[43]. The age of seizure onset was 13 years in both patients. Both had focal abdominal sensory seizures, incoherent speech, blurred vision, auditory hallucinations, slow ideation déjà vu and occasional FBCTS. Brain MRI findings were normal. Seizures were well controlled by ASMs.

ETL9, A DEPDC5- RELATED FTLE

In 2013, Shida *et al*[44] reported two families with TLE caused by *DEPDC5* gene heterogenous mutations. The patients had focal nonmotor and motor seizures and their interictal EEG showed slow waves and sharp waves in the temporal lobes[45]. *DEPDC5* proteins have no homology with ion channel proteins. *DEPDC5* protein formed a GATOR1 complex with NPRL2 and NPRL3, which inhibited the aggregation of mTORC1. In vitro, mutant mRNA products are degraded by the nonsense-mediated decay system, and *DEPDC5* haploinsufficiency was likely to be the cause of the disease [44]. Striano *et al*[46] detected a *DEPDC5* gene nonsense mutation, p.Tyr306*, in a family with two individuals diagnosed with MTLE. In the proband and her mother, the seizures were characterized by déjà vu, anxiety, derealization and epigastric sensation. During follow-up, the proband showed significant auditory seizures weekly, suggesting a diagnosis of LTLE[47]. The reports to date indicated that the phenotype of *DEPDC5*-related TLE was variable and that *DEPDC5* variants were responsible for both MTLE and LTLE.

ETL10, AN MICAL-1-RELATED FAMILIAL LTLE

Dazzo *et al*[48] identified three different *MICAL-1* gene heterozygous missense mutations in three LTE families without *LGII* or *RELN* gene mutations. The *MICAL-1* gene is expressed ubiquitously, with higher expression levels in the embryonic and nervous systems. In vitro, the variants significantly increased *MICAL-1* oxidoreductase activity and induced cell contraction, which likely resulted from deregulation of F-actin dynamics[49]. These results suggested that the dysregulation of actin cytoskeleton dynamics was a likely mechanism by which *MICAL-1* gene pathogenic variants led to LTE. The seizure onset age was 6-30 years, with most patients experiencing onset at 6-10 years. Affected individuals had auditory auras and some of them had aphasic symptoms. Most patients had FBCTS. EEG revealed temporal or fronto-temporal abnormal epileptic activity. Their 1.5-Tesla brain MRI scans were unremarkable. Seizures were well controlled with ASMs such as carbamazepine, methylhydantoin and vigabatrin.

ETL11, AN SCN1A-RELATED FTLE

In 2007, a southern Italian family was reported by Colosimo *et al*[50], in which 13 members over 3 generations had febrile seizures and TLE associated with the *SCN1A* p.M145T mutation. The *SCN1A* gene encodes the alpha subunit of the NaV1.1 sodium channel and is highly expressed in the central nervous system. *SCN1A* gene mutations were associated with a broad spectrum of epilepsy phenotypes and were commonly reported in epilepsies characterized by frequent febrile seizures during childhood; few had been reported in TLE[51]. The *SCN1A* p.M145T mutation was the first missense mutation found in DIS1 of *SCN1A* and caused a loss of function of the NaV1.1 channel

[52]. All 13 living members had febrile seizures onset from 5 to 45 mo. Nine subjects were affected with only febrile seizures and had normal EEG. Three individuals later developed TLE with epileptiform temporal spikes on EEG, and two of them had HS. The onset age of TLE was 10-13 years. Seizure types included focal seizures with or without awareness and rare nocturnal FBCTS. Seizures in the patient without HS were completely controlled with valproate. Seizures in 1 patient with HS were well controlled with the combination of carbamazepine and primidone. In another patient with HS, seizures continued despite treatment with the combination of topiramate and phenobarbital.

CONCLUSION

FTLE was always underestimated due to its heterogeneous intrafamily clinical manifestations. Some family members with subtle symptoms had not received a diagnosis of epilepsy prior to detailed enquiry by a neurologist[11]. Eleven types of FTLE have been identified thus far (Table 1).

In addition to typical temporal lobe seizures, special phenotypes also exist within some types of FTLE, such as migraine and febrile seizures. In 2000, Gambardella *et al* [53] reported a family with ETL4, in which migraine was a common phenotype among the TLE patients. Chr. 9q21-q22, harboring 604 genes, was correlated with both migraine and ETL4. Understanding of the pathogenetic mechanisms requires the identification of the genes responsible for the phenotype. ETL2, ETL5, ETL6 and ETL11 were associated with a high incidence of febrile seizures, which was also found to be a prominent feature in a number of genetically determined epilepsy cases[54]. Febrile seizures affect approximately 3% of children and increase the risk of developing HS [55]. Moreover, febrile seizures and TLE were associated with common genetic variation, such as the *CPA6* and *SCN1A* genes[36,56]. The prognosis of FTLE with a high incidence of febrile seizures was almost good. However, in some patients with genetically based MTLE-HS and histories of febrile seizures, the prognosis was poor, and the underlying pathogenic genes remain unknown[57]. A growing number of studies had proven that HS and MTLE had polygenic or multifactorial modes of inheritance. The mechanism involves neuron development, differentiation, synaptic signaling, immune response and vascular development, which might provide directions for therapy of MTLE-HS[19].

LTLE was mostly genetic in etiology related to *LG11*, *RELN*, *MICAL-1* and *DEPDC5* gene mutations. *LG11* and *RELN* mutations were reported in approximately 35 and 17.5 % of LTLE families respectively[12,38]. The phenotypes of familial LTLE caused by pathogenic mutations of the *LG11*, *RELN* and *MICAL-1* genes were similar. However, the molecular functions of these genes were discrepant, indicating that the mechanism of LTLE was complicated. Notably, some candidate loci were also gradually being recognized, such as the Chr 9q13.11-q13.31 Locus (not mentioned above), which was related to familial LTLE with a higher frequency of febrile seizures and migraine and a lower recurrence of focal to bilateral seizures than ETL1, ETL7 and ETL10[58].

Four gene loci on Chr 12q22-q23.3, 4q13.2-q21.3, 9q21-q22, and 3q25-q26, were closely related to FTLE. These loci each contain 280-604 genes, but the specific pathogenic genes for TLE had not yet been identified. Reports on each type of FTLE were rare, which limits our knowledge and hinders in-depth research. Reaching a complete understanding of the genetics of TLE is still a long-term prospect.

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