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Review Article

Genetics of Temporal Lobe Epilepsy: A Review

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Temporal lobe epilepsy (TLE) is usually regarded as a polygenic and complex disorder. To understand its genetic component, numerous linkage analyses of familial forms and association studies of cases versus controls have been conducted since the middle of the nineties. The present paper lists genetic findings for TLE from the initial segregation analysis to the most recent results published in May 2011. To date, no genes have been clearly related to TLE despite many efforts to do so. However, it is vital to continue replication studies and collaborative attempts to find significant results and thus determine which gene variant combination plays a definitive role in the aetiology of TLE.

1. Introduction

Temporal lobe of epilepsy (TLE) is known to be the most common form of partial epilepsy and accounts for 60% of seizures [1]. Depending on the seizure origin, TLE should be subdivided into mesial, lateral, and neocortical. Partial epilepsies are often associated with antecedent of brain injury, such as head trauma, stroke, or infection, and are therefore classified as "symptomatic" [1]. The term "cryptogenic" is related to syndromes where there is insufficient evidence to assign a specific aetiology, whereas "idiopathic" partial epilepsy is associated with a putative genetic origin [1]. Family studies have shown that relatives of patients with epilepsy are at higher risk of suffering from seizures compared to relatives of controls [2, 3]. Moreover, relatives of patients with focal temporal EEG abnormalities have generally been found to have higher risks of EEG abnormalities which seem to be caused by an autosomal dominant gene [4]. Therefore, various susceptibility genes and environmental factors are believed to be involved in the aetiology of TLE, which is considered to be a heterogeneous, polygenic, and complex disorder. However, few families with a monogenic type of TLE [5] have been reported. To date, only a few chromosomal localisations and genes have been involved in TLE.

2. Methods

In the present paper, PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez) was used as a search engine with no language restrictions from its creation to May 15, 2011. Searching strategy was for linkage analysis ("epilepsy, temporal lobe" [MeSH Terms] OR ("epilepsy" [All Fields] AND "temporal" [All Fields] AND "lobe" [All Fields]) OR "temporal lobe epilepsy" [All Fields] OR ("temporal" [All Fields] AND "lobe" [All Fields] AND "epilepsy" [All Fields])) AND ("genetic linkage" [MeSH Terms] OR ("genetic" [All Fields] AND "linkage" [All Fields]) OR "genetic linkage" [All Fields]) and for association studies ("epilepsy, temporal lobe" [MeSH Terms] OR ("epilepsy" [All Fields] AND "temporal" [All Fields] AND "lobe" [All Fields]) OR "temporal lobe epilepsy" [All Fields] OR ("temporal" [All Fields] AND "lobe" [All Fields] AND "epilepsy" [All Fields])) AND ("association" [MeSH Terms] OR "association" [All Fields]) AND ("clinical trials as topic" [MeSH Terms] OR ("clinical" [All Fields] AND "trials" [All Fields] AND "topic" [All Fields]) OR "clinical trials as topic" [All Fields] OR "study" [All Fields] OR "biomedical research" [MeSH Terms] OR ("biomedical" [All Fields] AND "research" [All Fields]) OR "biomedical research" [All Fields]). All the references cited in this paper were reviewed to identify additional works not

indexed by the database selected. Suitable studies had to be independent studies using original data which had been published in a peer-review journal.

3. Familial Monogenic Temporal Lobe Epilepsy

3.1. Autosomal Dominant Lateral Temporal Epilepsy (ADLTE). The first localisation of ADLTE or autosomal dominant partial epilepsy with auditory features (ADPEAF) was established on chromosome 10q by linkage analysis in a three-generation family with 11 affected individuals. This family showed an autosomal dominant segregation of the phenotype with reduced penetrance [6]. Subsequent families with similar clinical descriptions were linked to the same chromosomal region [7, 8]. This locus was also linked to ADPEAF in 5 other families [9, 10]. This well-established chromosome 10q24 locus contains leucine-rich, glioma-inactivated 1 (*LGI1*) gene, which has a putative role in development [11]. Kalachikov and colleagues were the first to describe 5 *LGI1* mutations in five ADLTE families with auditory features (Table 1) [11]. After these initial results, numerous different *LGI1* mutations have been linked to ADLTE (Table 1). Interestingly, 50% of ADLTE families did not show any *LGI1* mutations [12]. Moreover, *de novo LGI1* mutations in unrelated sporadic TLE cases with auditory features, also called idiopathic partial epilepsy with auditory features (IPEAF) [13], account for about 2% of cases only [14]. A recent study, evaluating *LGI1* promoter, *prodynorphin* (*PDYN*), and *GABA (B) receptor 1* (*GABBR1*) genes in 104 sporadic IPEAF, did not show any statistically significant differences between patients and controls [15].

3.2. Pure Familial Mesial Temporal Lobe Epilepsy (FMTLE). FMTLE is a benign syndrome, which is not associated with hippocampal sclerosis (HS) or febrile seizure (FS). The main symptoms are aura with prominent psychic and autonomic features and *déjà vu* and *jamais vu* [33]. This disorder shows an autosomal dominant mode of inheritance with incomplete penetrance in a three-generation Italian family with 8 affected people [34]. A few large pedigrees have been published and only one linkage has been found on chromosome 4q13.2–21.3 in a four-generation family with 12 patients [35]. To date, no mutated gene has been linked to FMTLE.

3.3. Febrile Seizures, Hippocampal Sclerosis, and Familial Temporal Lobe Epilepsy. Many studies have shown that FS, HS and familial TLE are closely interconnected [36–39]. MRI studies of TLE families have shown not only that hippocampal abnormalities are the consequence of repeated seizures but also that genetic mechanisms could play a significant role in their development of hippocampal damage [40]. Therefore, genetic predisposition seems to be a key causal factor for HS and for specific subsyndromes displaying FS [41–43]. The familial syndrome called genetic epilepsy with febrile seizure plus (GEFS$^+$) [44] exemplifies these links. A large study of 9 GEFS$^+$ families showed that two of them included TLE patients [45]. Furthermore, another GEFS$^+$ family with TLE showed a mutation in the *SCN1A* gene (Table 1) [31], initially linked to GEFS$^+$ pedigree without partial epilepsy [46]. More recently, Scheffer and colleagues reported three TLE and GEFS$^+$ families with specific mutations in the *SCN1B* gene (Table 1) [32], which was initially linked to a pure GEFS$^+$ pedigree [47]. Linkage analysis of two FS families with TLE showed evidence for digenic inheritance on chromosomes 18qter and 1q25–31 [48] and on chromosomes 3p23–24.2 and 18p [49]. A particular gypsy family from an isolated founder population was linked to chromosome 5q31.3–32. The affected individuals suffered from TLE associated with FS with mild intellectual deficit [50]. Recently, a FS family with two patients with possible benign TLE showed a putative new linkage to chromosome 17q12–14 [51]. Even though the literature reported some chromosomal localisation and gene mutations, some TLE families with FS and HS were not linked to any loci or genes [28, 52, 53]. These findings indicate that familial TLE is genetically heterogeneous.

4. Sporadic TLE Cases

As suggested by segregation and linkage studies, TLE could be considered to be a complex disorder. Therefore, association study has been proposed as the method of choice in understanding the genetic background of TLE in sporadic cases [54]. However, this proposal remains controversial [55] because replication studies of the first-positive association often revealed conflicting results. To date, no genes have been clearly associated with sporadic cases of TLE as presented in this paper. All association studies cited in the text below are shown in Table 2 that contains genetic variation counts and ethnicity of samples. The term of "replication study" was used only if the following study was conducted in the same group or subgroup of patients with the same ethnicity as the original one. Every study cited below assessed DNA extracted from peripheral blood.

4.1. γ-Aminobutyric Acid B Receptor 1 (GABBR1). GABBR1 gene encodes one subunit of the GABA (B) receptor, and higher levels of *GABBR1* mRNA have been found in hippocampal resection of TLE patients with HS as compared to postmortem controls [88]. On this basis, Gambardella and colleagues assessed a missense mutation in exon 7 of *GABBR1*, c.1465G>A (p.Gly489Ser) in sporadic cases of TLE in Caucasians. They found a significant association, which displayed an increased level of heterozygosity in patients compared to the controls [56]. Subsequent studies did not find this initial positive result [5, 57–60], even in Chinese populations [61, 62]. Only one study yielded similar results to those obtained by Gambardella and colleagues in an Argentinean population. The authors proposed that this significant replication was given by the migration of Italian people in Argentina [63].

4.2. γ-Aminobutyric Acid B Receptor 2 (GABBR2). GABBR2 gene encodes another subunit of the GABA (B) receptor. A positive association was found in the Chinese population

Table 1: Genomic variations linked to familial TLE.

Gene	Genomic variation	Protein alteration	Accession number	Type of TLE	Reference
LGI1	c.1639insA	Frameshift, protein truncation	CI020606	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
LGI1	c.611delC (835delC)	Frameshift, protein truncation	CD020573	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
LGI1	c.136-3C>A (359-3C>A)	Intron retention, protein truncation	CM022035	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
LGI1	c.1050-1051delCA	Frameshift, protein truncation	CD020574	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
LGI1	c.1148A>C	p.Glu383Ala	rs28937874	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
LGI1	c.758delC	Frameshift, protein truncation	CD021020	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16]
LGI1	c.1420C>T	Premature stop codon, protein truncation	CM020950	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16] Bisulli et al. 2004 [13]
LGI1	c.136T>C	p.Cys46Arg	rs104894166	ADLTE/ADPEAF	Gu et al. 2002 [17]
LGI1	c.953T>G	p.Phe318Cys	rs28939075	ADLTE/ADPEAF	Fertig et al. 2003 [18]
LGI1	c.598T>C	p.Cys200Arg	CM034239	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
LGI1	c.1295T>A	p.Val432Glu	CM034240	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
LGI1	Unknown	p.Leu26Arg	Unknown	ADLTE/ADPEAF	Pizzuti et al. 2003 [20]
LGI1	c.839-2A>C	Intron retention, protein truncation	Unknown	ADLTE/ADPEAF	Kobayashi et al. 2003 [21]
LGI1	c.124T>G	p.Cys42Gly	CM041029	ADLTE/ADPEAF	Berkovic et al. 2004 [22]
LGI1	c.1418C>T	p.Ser473Leu	CM041033	ADLTE/ADPEAF	Berkovic et al. 2004 [22] Kawamata et al. 2010 [23]
LGI1	c.124T>C (348T>C)	p.Cys42Arg	CM041030	ADLTE/ADPEAF	Ottman et al. 2004 [24]
LGI1	c.893T>C	p.Ile298Thr	CM041032	ADLTE/ADPEAF	Ottman et al. 2004 [24]
LGI1	c.329C>A	p.Ala110Asp	CD044789	ADLTE/ADPEAF	Ottman et al. 2004 [24]
LGI1	c.329delC	Frameshift, protein truncation	CD044789	ADLTE/ADPEAF	Hedera et al. 2004 [25]
LGI1	c.435C>G	p.Ser145Arg	CM044660	ADLTE/ADPEAF	Hedera et al. 2004 [25]
LGI1	c.461T>C	p.Leu154Pro	CM055408	ADLTE/ADPEAF	Pisano et al. 2005 [26]
LGI1	c.406C>T	p.Arg136Trp	rs119488099	ADLTE/ADPEAF	Michelucci et al. 2007 [14]
LGI1	c.431+1G>A	Deletion, protein truncation	Unknown	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
LGI1	c.695T>C	p.Leu232Pro	rs104894167	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
LGI1	c.365T>A	p.Ile122Lys	rs119488100	ADLTE/ADPEAF	Striano et al. 2008 [28]
LGI1	c.367G>A	p.Glu123Lys	Unknown	ADLTE/ADPEAF	Bonaventura et al. 2009 [29]

Table 1: Continued.

Gene	Genomic variation	Protein alteration	Accession number	Type of TLE	Reference
LGI1	c.1421G>A	p.Arg474Glu	CM020950	ADLTE/ADPEAF	Kawamata et al. 2010 [23]
LGI1	c.1219C>T	p.Arg407Cys	Unknown	ADLTE/ADPEAF	Striano et al. 2011 [30]
SCN1A	c.3809A>C	p.Lys1270Thr	rs121918626	TLE + GEFS$^+$	Abou-Khalil et al. 2001 [31]
SCN1B	c.363C>G	p.Cys121Trp	rs104894718	TLE + GEFS$^+$	Scheffer et al. 2007 [32]
SCN1B	Unknown	p.Arg85Cys	CM071081	TLE + GEFS$^+$	Scheffer et al. 2007 [32]
SCN1B	Unknown	p.Arg85His	CM071082	TLE + GEFS$^+$	Scheffer et al. 2007 [32]

for the rs967932 A-allele of *GABBR2*, which increased the risk of TLE in patients [62]. Moreover, a particular haplotype of *GABBR2* (G-C-A-C, rs3780428-rs1999501-rs967932-rs944688, resp.) occurred more frequently in cases than in controls (12.26% and 6.51%, resp., $P = 0.0004$) [62]. In addition, TLE patients with this haplotype showed an earlier onset of the disease. So far, these results have not been confirmed in other independent groups of sporadic TLE.

4.3. Prodynorphin (PDYN). PDYN, the precursor of the dynorphin opioid peptides, is wildly expressed in the central nervous system (CNS). Its promoter showed a 68-bp tandem repeat containing one binding site per repeat for the transcription factor AP-1 [89]. Three or four repeats, named H-allele, are associated with a significant increase in gene expression, whereas one or two repeat(s), named the L-allele, cannot be stimulated over basal conditions [89]. A first association study showed that the L-allele of the variable number of tandem repeats (VNTR) of *PDYN* promoter is a risk factor for TLE in patients with a family history of seizures [64]. This result was not replicated in 4 independent studies of the Caucasian population with TLE [5, 65–68].

4.4. Apolipoprotein E (ApoE). ApoE is a constitutive protein of the triglyceride-rich lipoproteins, very-low-density lipoprotein, and chylomicrons and plays a role in lipoprotein metabolism [90]. *ApoE* gene encodes 3 protein isoforms: $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. In a first association study, the $\varepsilon 4$ isoform was not associated with an early age of onset of TLE [69], but the association was found to be statistically significant in a second study [70]. Subsequently, five other replication studies were conducted [5, 67, 71–73] and only one of them found the same association in the same direction [67]. Other subtypes of TLE were considered to be associated with the ApoE $\varepsilon 4$ isoform. A study evaluating the memory in cases of mild, well-controlled nonlesional TLE found that $\varepsilon 4$ carriers showed a verbal learning deficit compared to noncarriers (50% and 19%, resp., $P = 0.004$) [71]. A subsequent very similar study demonstrated that patients with medically intractable TLE and a long history of epilepsy had the poorest memory performance if they carried the $\varepsilon 4$ allele ($P < 0.01$) [91]. Two additional studies evaluated the relationship between the *ApoE* $\varepsilon 4$ allele and postictal confusion in medically intractable TLE. Results were inconsistent. Chapin and colleagues found an association (68% of $\varepsilon 4^+$ and 43% of $\varepsilon 4^-$, $P = 0.04$) [92], whereas Kauffman and coworkers did not (30.4% of $\varepsilon 4^+$ and 46.3% of $\varepsilon 4^-$, $P = 0.2$) [93]. A final study investigated if *ApoE* $\varepsilon 4$ allele is associated with increased risk of late onset posttraumatic seizures, early onset, refractory complex partial seizures (CPSs), and postictal confusion in a Chinese population with TLE. They found a significant association between prior trauma and $\varepsilon 4$ allele in their TLE patients only (20.7% of $\varepsilon 4^+$ and 12.1% of $\varepsilon 4^-$, $P = 0.023$) [94].

4.5. Interleukin 1α (IL-1α). IL-1α is a major proinflammatory cytokine, which is synthesized during infection and inflammatory processes [90]. A single nucleotide polymorphism (SNP) on *IL-1α* 5′UTR (*IL-1α*−889) was genotyped in some subgroups of TLE: with or without HS (TLE-HS$^{+/-}$) [74] and with or without FS (TLE-FS$^{+/-}$) [75]. No associations were found. A third team found three statistically positive associations. Genotype 1-1 was more frequently displayed in the TLE group and in subgroups of TLE-HS$^+$ and TLE-FS$^-$ [67].

4.6. Interleukin 1RA (IL-1RA). IL-1RA is an antagonist that competes for the same IL-1 receptor as for IL-1α [74]. A VNTR on *IL-1RA* intron 2 (*IL-1RA*-int2) was associated with TLE-HS$^-$. Allele 1 and genotype 1-1 showed lower frequencies, while allele 2 and genotypes 1-2 and 2-2 showed higher frequencies in TLE-HS$^-$ patients than in controls [67]. The primary study failed to show any association [74].

4.7. Interleukin 1β (IL-1β). IL-1β is another major proinflammatory cytokine and acts on the same IL-1 receptor as IL-1α [74]. Two SNPs (*IL-1β*−511 and *IL-1β*+3953) were studied by Kanemoto and colleagues in TLE-HS$^{+/-}$ patients. For *IL-1β*−511, they found a high frequency of genotype 2-2 in TLE-HS$^+$ compared to the controls [74] and confirmed their result in a larger sample [76]. This association was

Table 2: Genomic variations associated which sporadic TLE cases.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
GABBR1	c.1465G>A → p.Gly489Ser	Gambardella et al. 2003 [56]	Nonlesional TLE	Caucasian	*n* = 141	*n* = 372	*<0.0001*
	(CM031183)	Initial study			A/A = 0 (0.0) A/G = 24 (17.0) G/G = 117 (83.0)	A/A = 0 (0.0) A/G = 2 (0.5) G/G = 370 (99.5)	
		Cavalleri et al. 2005 [5] Replication study	Nonlesional TLE	Caucasian	*n* = 245 A/A = 0 (0.0) A/G = 2 (1.0) G/G = 218 (99.0)	*n* = 1089 A/A = 0 (0.0) A/G = 8 (1.0) G/G = 1062 (99.0)	NS
		Ma et al. 2005 [57]	TLE-FS$^+$	Caucasian	*n* = 120 A/A = 0 (0.0) A/G = 1 (0.84) G/G = 119 (99.16)	*n* = 118 A/A = 1 (0.85) A/G = 0 (0.0) G/G = 117 (99.15)	NS
		Salzmann et al. 2005 [58] Replication study	Nonlesional TLE	Caucasian	*n* = 110 A/A = (0.0) A/G = 2 (1.82) G/G = 108 (98.18)	*n* = 145 A/A = (0.0) A/G = (0.0) G/G = 145 (100)	NS
		Tan et al. 2005 [59] Replication study	Nonlesional TLE	Caucasian	*n* = 234 A/A = (0.0) A/G = 1 (0.4) G/G = 233 (99.6)	*n* = 164 A/A = (0.0) A/G = 1 (0.6) G/G = 163 (99.4)	NS
		Stögmann et al. 2006 [60]	TLE	Caucasian	*n* = 188 A/A = 0 (0.0) A/G = 2 (1.1) G/G = 186 (98.9)	*n* = 259 A/A = 0 (0.0) A/G = 0 (0.0) G/G = 259 (100)	NS
		Ren et al. 2005 [61]	Nonlesional TLE	Chinese	*n* = 112 A/A = 0 (0.0) A/G = 0 (0.0) G/G = 112 (100)	*n* = 124 A/A = 0 (0.0) A/G = 0 (0.0) G/G = 124 (100)	NS
		Wang et al. 2008 [62]	TLE	Chinese	*n* = 315 A/A = 0 (0.0) A/G = 0 (0.0) G/G = 315 (100)	*n* = 318 A/A = 0 (0.0) A/G = 0 (0.0) G/G = 318 (100)	NS
		Kauffman et al. 2008 [63]	TLE-HS$^+$	Argentinean	*n* = 102 A/A = 0 (0.0) A/G = 49 (48.0) G/G = 53 (52.0)	*n* = 71 A/A = 0 (0.0) A/G = 6 (8.5) G/G = 65 (91.5)	$3.788e^{-8}$

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
GABBR2	G>A → intron 1 (rs967932)	Wang et al. 2008 [62] Initial study	TLE	Chinese	*n* = 315 A/A = 72 (22.64) A/G = 164 (51.57) G/G = 82 (25.79)	*n* = 318 A/A = 63 (20.0) A/G = 136 (43.17) G/G = 116 (36.83)	*0.003*
PDYN	68 bp tandem repeat → promoter H-allele = 3 or 4 repeats L-allele = 1 or 2 repeats (rs71193945)	Stögmann et al. 2002 [64] Initial study	Nonlesional TLE, familial risk	Caucasian	*n* = 43 L/L = 10 (23.3) L/H = 23 (53.5) H/H = 10 (23.3)	*n* = 202 L/L = 18 (8.9) L/H = 88 (43.6) H/H = 96 (47.5)	*0.005*
		Gambardella et al. 2003 [65] Replication study	Nonlesional TLE, familial risk	Caucasian	*n* = 115 L/L = 9 (7.8) L/H = 40 (34.8) H/H = 66 (57.4)	*n* = 259 L/L = 16 (6.2) L/H = 105 (40.5) H/H = 138 (53.3)	NS
		Tilgen et al. 2003 [66] Replication study	Nonlesional TLE, familial risk	Caucasian	*n* = 46 L/L = 3 (7.0) L/H = 21 (45.0) H/H = 22 (48.0)	*n* = 205 L/L = 22 (11.0) L/H = 84 (41.0) H/H = 99 (48.0)	NS
		Cavalleri et al. 2005 [5] Replication study	Nonlesional TLE, familial risk	Caucasian	*n* = 50 L/L = 8 (17.0) L/H = 22 (47.0) H/H = 17 (36.0)	*n* = 384 L/L = 30 (8.0) L/H = 160 (44.0) H/H = 175 (48.0)	NS
		Salzmann et al. 2008 [67] Replication study	Nonlesional TLE, familial risk	Caucasian	*n* = 21 L/L = 2 (9.5) L/H = 11 (52.4) H/H = 8 (38.1)	*n* = 206 L/L = 14 (6.8) L/H = 78 (37.9) H/H = 114 (55.3)	NS
		Kauffman et al. 2008 [68]	Nonlesional TLE, familial risk	Argentinean	*n* = 18 L/L = 1 (5.5) L/H = 8 (44.5) H/H = 9 (50.0)	*n* = 86 L/L = 8 (9.3) L/H = 37 (43.0) H/H = 41 (47.7)	NS
ApoE	Isoform ε4 (CI056481)	Gambardella et al. 1999 [69] Initial study	Nonlesional TLE	Caucasian	*n* = 63 $\varepsilon4^+$ = 5; years not indicated $\varepsilon4^-$ = 58; years not indicated		NS

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
		Briellmann et al. 2000 [70] Replication study	Early onset of TLE associated with $\varepsilon 4$	Caucasian	$n = 43$ $\varepsilon 4^+ = 10$; 5 ± 5 years $\varepsilon 4^- = 33$; 10 ± 15 years		*0.004*
		Cavalleri et al. 2005 [5] Replication study	Early onset of TLE associated with $\varepsilon 4$	Caucasian	$n = 181$ $\varepsilon 4^+ = 30$; 13.7 ± 10 years $\varepsilon 4^- =$ 151; 16.7 ± 11 years		NS
		Gambardella et al. 2005 [71] Replication study	Early onset of TLE associated with $\varepsilon 4$	Caucasian	$n = 13$ $\varepsilon 4^+ = 24$; 26.2 ± 20.1 years $\varepsilon 4^- = 114$; 33.9 ± 20.7 years		NS
		Yeni et al. 2005 [72]	Early onset of TLE-HS$^+$ associated with $\varepsilon 4$	Turkish	$n = 47$ $\varepsilon 4^+ = 8$; 7.44 ± 6.13 years $\varepsilon 4^- = 39$; 8.75 ± 7.61 years		NS
		Salzmann et al. 2008 [67] Replication study	Early onset of TLE associated with $\varepsilon 4$	Caucasian	$n = 106$ $\varepsilon 4^+ = 26$; 10.54 ± 6.36 years $\varepsilon 4^- = 80$; 16.51 ± 9.90 years		*0.003*
		Kauffman et al. 2010 [73]	Early onset of TLE-HS$^+$ associated with $\varepsilon 4$	Argentinean	$n = 78$ $\varepsilon 4^+ = 23$; 14.3 ± 12.13 years $\varepsilon 4^- = 55$; 16.5 ± 12.54 years		NS
IL-1α	c.−889C>T → promoter Allele 1 = C Allele 2 = T (unknown)	Kanemoto et al. 2000 [74] Initial study	TLE-HS$^{+/-}$	Japanese	TLE-HS$^+$ $n = 50$ 1/1 = 38 (76.0) 1/2 = 10 (20.0) 2/2 = 2 (4.0)	$n = 112$ 1/1 = 87 (77.7) 1/2 = 25 (22.3) 2/2 = 0 (0.0)	TLE-HS$^+$ versus controls = NS

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
					TLE-HS$^-$		TLE-HS$^-$ versus
					$n = 53$		controls = NS
					1/1 = 44 (83.0)		
					1/2 = 8 (15.1)		
					2/2 = 1 (1.9)		
		Ozkara et al. 2006 [75]	TLE-HS$^+$	Turkish	$n = 47$	$n = 99$	NS
					1/1 = 23 (48.9)	1/1 = 37 (37.3)	
					1/2 = 23 (48.9)	1/2 = 52 (52.5)	
					2/2 = 1 (2.1)	2/2 = 10 (10.1)	
		Ozkara et al. 2006 [75] Initial study	TLE-FS$^{+/-}$	Turkish	TLE-FS$^+$		TLE-FS$^+$ versus
					$n = 28$		TLE-FS$^-$ = NS
					1/1 = 16 (57.1)		
					1/2 = 12 (42.8)		
					2/2 = 0 (0.0)		
					TLE-FS$^-$		
					$n = 19$		
					1/1 = 9 (47.3)		
					1/2 = 10 (52.6)		
					2/2 = 0 (0.0)		
		Salzmann et al. 2008 [67]	TLE-HS$^{+/-}$	Caucasian	TLE-HS$^+$	$n = 235$	TLE-HS$^+$ versus
					$n = 86$	1/1 = 99 (42.1)	controls = *0.027*
					1/1 = 50 (58.1)	1/2 = 118 (50.2)	
					1/2 = 29 (33.7)	2/2 = 8 (7.7)	
					2/2 = 7 (8.1)		
					TLE-HS$^-$		TLE-HS$^-$ versus
					$n = 23$		controls = NS
					1/1 = 15 (65.2)		
					1/2 = 7 (30.4)		
					2/2 = 1 (4.4)		
			TLE-FS$^-$	Caucasian	TLE-FS$^-$		TLE-FS$^+$ versus
					$n = 54$		controls =*0.0078*
					1/1 = 33 (61.1)		
					1/2 = 16 (29.6)		
					2/2 = 5 (9.3)		

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
IL-1RA	86 bp tandem repeat → intron 2	Kanemoto et al. 2000 [74]	TLE-HS$^{+/-}$	Japanese	TLE-HS^{+}	$n = 112$	TLE-HS^{+} versus
	Allele 4 = 5 repeats	Initial study			$n = 50$	1/1 = 102 (91.9)	controls = NS
	Allele 1 = 4 repeats				1/1 = 46 (92.0)	1/2 = 6 (5.4)	
	Allele 2 = 2 repeats				1/2 = 3 (6.0)	1/3 = 1 (0.9)	
	Allele 3 = 3 repeats				1/3 = 1 (2.0)	1/4 = 2 (1.8)	
	Allele 5 = 6 repeats (rs2234663)				1/4 = 0 (0.0)		
					TLE-HS^{-}		TLE-HS^{-} versus
					$n = 53$		controls = NS
					1/1 = 52 (98.1)		
					1/2 = 1 (1.9)		
					1/3 = 0 (0.0)		
					1/4 = 0 (0.0)		
		Salzmann et al. 2008 [67]	TLE-HS$^{+/-}$	Caucasian	TLE-HS^{+}	$n = 242$	TLE-HS^{+} versus
					$n = 86$	1/1 = 128 (52.9)	controls = NS
					1/1 = 43 (50.0)	1/2 = 90 (37.2)	
					1/2 = 36 (41.9)	1/4 = 5 (2.1)	
					1/4 = 1 (1.2)	1/5 = 0 (0.0)	
					1/5 = 0 (0.0)	2/2 = 16 (6.6)	
					2/2 = 6 (7.0)	2/4 = 3 (1.2)	
					2/4 = 0 (0.0)		
					TLE-HS^{-}		TLE-HS^{-} versus
					$n = 23$		controls = *0.001*
					1/1 = 5 (21.7)		
					1/2 = 13 (56.5)		
					1/4 = 0 (0.0)		
					1/5 = 1 (4.3)		
					2/2 = 4 (17.4)		
					2/4 = 0 (0.0)		
IL-1β	c.−511C>T → promoter	Kanemoto et al. 2000 [74]	TLE-HS$^{+/-}$	Japanese	TLE-HS^{+}	$n = 112$	TLE-HS^{+} versus
	Allele 1 = C	Initial study			$n = 50$	1/1 = 31 (27.7)	controls =*0.0085*
	Allele 2 = T (rs1799916)				1/1 = 9 (18.0)	1/2 = 58 (51.8)	
					1/2 = 19 (38.0)	2/2 = 23 (20.5)	
					2/2 = 22 (44.0)		
					TLE-HS^{-}		TLE-HS^{-} versus
					$n = 53$		controls = NS
					1/1 = 13 (24.5)		
					1/2 = 30 (56.6)		
					2/2 = 10 (18.9)		

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
		Kanemoto et al. 2003 [76] 16 TLE-HS$^+$ and 11 TLE-HS$^-$ were added to initial study [74]	TLE-HS$^{+/-}$	Japanese	TLE-HS$^+$		
					n = 66	*n* = 163	TLE-HS$^+$ versus controls =*0.0028*
					1/1 = 12(18.2)	1/1 = 44 (27.0)	
					1/2 = 24 (36.4)	1/2 = 82 (50.3)	
					2/2 = 30 (45.5)	2/2 = 37 (22.7)	
					TLE-HS$^-$		
					n = 64		TLE-HS$^-$ versus controls = NS
					1/1 = 16 (25.0)		
					1/2 = 36 (56.3)		
					2/2 = 12 (18.7)		
		Heils et al. 2000 [77]	TLE-HS$^+$	Caucasian	*n* = 86	*n* = 133	NS
					1/1 = 33 (38.0)	1/1 = 57 (42.0)	
					1/2 = 42 (49.0)	1/2 = 60 (45.0)	
					2/2 = 11 (13.0)	2/2 = 16 (12.0)	
		Buono et al. 2001 [78]	TLE-HS$^+$	Caucasian	*n* = 61	*n* = 119	NS
					1/1 = 31 (50.8)	1/1 = 44 (37.0)	
					1/2 = 24 (39.3)	1/2 = 68 (57.1)	
					2/2 = 6 (9.8)	2/2 = 7 (5.9)	
		Jin et al. 2003 [79]	TLE-HS$^{+/-}$	Chinese	TLE-HS$^+$		
					n = 67	*n* = 115	TLE-HS$^+$ versus controls = NS
					1/1 = 16 (24.0)	1/1 = 26 (23.0)	
					1/2 = 32 (48.0)	1/2 = 62 (54.0)	
					2/2 = 19 (28.0)	2/2 = 27 (23.0)	
					TLE-HS$^-$		
					n = 45		TLE-HS$^-$ versus controls = NS
					1/1 = 12 (27.0)		
					1/2 = 24 (53.0)		
					2/2 = 9 (20.0)		
		Cavalleri et al. 2005 [5]	TLE-HS$^+$	Caucasian	*n* = 141	*n* = 384	NS
					1/1 = 59 (45.0)	1/1 = 161 (44.0)	
					1/2 = 57 (44.0)	1/2 = 162 (45.0)	
					2/2 = 15 (11.0)	2/2 = 41 (11.0)	
		Ozkara et al. 2006 [75]	TLE-HS$^+$	Turkish	*n* = 47	*n* = 99	NS
					1/1 = 16 (34.0)	1/1 = 41 (41.4)	
					1/2 = 21 (44.6)	1/2 = 41 (41.4)	
					2/2 = 10 (21.2)	2/2 = 17 (17.1)	
		Ozkara et al. 2006 [75] Initial study	TLE-FS$^{+/-}$	Turkish	TLE-FS$^+$		
					n = 28		TLE-FS$^+$ versus TLE-FS$^-$ = NS
					1/1 = 9 (32.1)		
					1/2 = 13 (46.4)		
					2/2 = 6 (21.4)		
					TLE-FS$^-$		
					n = 19		
					1/1 = 5 (26.3)		
					1/2 = 9 (47.3)		
					2/2 = 5 (26.3)		

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
		Salzmann et al. 2008 [67]	TLE-HS$^{+/-}$	Caucasian	TLE-HS^{+} *n* = 86 1/1 = 35 (40.7) 1/2 = 45 (52.3) 2/2 = 6 (7.0)	*n* = 227 1/1 = 99 (43.6) 1/2 = 108 (47.6) 2/2 = 20 (8.8)	TLE-HS^{+} versus controls = NS
					TLE-HS^{-} *n* = 23 1/1 = 12 (52.2) 1/2 = 9 (39.1) 2/2 = 2 (8.7)		TLE-HS^{-} versus controls = NS
IL-1β	IL-1β + 3953 → exon 5 Allele 1 and allele 2 (CM040228)	Kanemoto et al. 2000 [74] Initial study	TLE-HS$^{+/-}$	Japanese	TLE-HS^{+} *n* = 50 1/1 = 45 (90.0) 1/2 = 5 (10.0) 2/2 = 0 (0.0)	*n* = 112 1/1 = 105 (93.8) 1/2 = 7 (6.3) 2/2 = 0 (0.0)	TLE-HS^{+} versus controls = NS
					TLE-HS^{-} *n* = 53 1/1 = 49 (92.5) 1/2 = 3 (5.7) 2/2 = 1 (1.9)		TLE-HS^{-} versus controls = NS
		Ozkara et al. 2006 [75]	TLE-HS^{+}	Turkish	*n* = 47 1/1= 28 (59.5) 1/2 = 18 (38.2) 2/2 = 1 (2.1)	*n* = 99 1/1= 63 (63.6) 1/2 = 30 (30.3) 2/2 = 17 (17.1)	NS
		Ozkara et al. 2006 [75] Initial study	TLE-FS$^{+/-}$	Turkish	TLE-FS^{+} *n* = 28 1/1 = 19 (67.8) 1/2 = 9 (32.1) 2/2 = 0 (0.0)		TLE-FS^{+} versus TLE-FS^{-} = NS
					TLE-FS^{-} *n* = 19 1/1 = 12 (63.1) 1/2 = 7 (36.8) 2/2 = 0 (0.0)		

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
		Salzmann et al. 2008 [67]	TLE-HS$^{+/-}$	Caucasian	TLE-HS^{+} *n* = 86 1/1 = 45 (52.3) 1/2 = 34 (39.5) 2/2 = 7 (8.2) TLE-HS^{-} *n* = 23 1/1 = 14 (60.9) 1/2 = 8 (34.8) 2/2 = 1 (4.3)	*n* = 234 1/1 = 118 (50.4) 1/2 = 101 (43.2) 2/2 = 15 (6.4)	TLE-HS^{+} versus controls = NS TLE-HS^{-} versus controls = NS
PRNP	p.Asn171Ser (CM971239)	Walz et al. 2003 [80] Initial study	Refractory TLE-HS^{+}	Brazilian	Seizure-free *n* = 85 Asn/Asn = 70 (82.4) Asn/Ser = 15 (17.6) Seizure *n* = 13 Asn/Asn = 6 (46.2) Asn/Ser = 7 (53.8)		Seizure-free versus Seizure = *0.005*
		Cavalleri et al. 2005 [5]	Refractory TLE-HS^{+}	Caucasian	*n* = 121 Asn/Asn = 109 (100) Asn/Ser = 0 (0.0) Ser/Ser = 0 (0.0)	*n* = 384 Asn/Asn = 360 (99.8) Asn/Ser = 1 (0.2) Ser/Ser = 0 (0.0)	NS
PRNP	p.Met129Val (CM890104)	Labate et al. 2007 [81] Initial study	Women, nonlesional TLE	Caucasian	*n* = 162 Met/Met = 64 (39.5) Met/Val = 77 (47.5) Val/Val = 21 (13.0)	*n* = 141 Met/Met = 77 (54.6) Met/Val = 54 (38.3) Val/Val = 10 (7.1)	*0.021*
		Wang et al. 2008 [82]	Women, nonlesional TLE	Chinese	*n* = 150 Met/Met = 146 (97.33) Met/Val = 4 (2.67) Val/Val = 0 (0.0)	*n* = 312 Met/Met = 302 (96.79) Met/Val = 10 (3.31) Val/Val = 0 (0.0)	NS
5-HTT	5-HTTLPR ins/del → 5′UTR S-allele = short variant L-allele = long variant (rs12720056)	Manna et al. 2007 [83] Initial study	Nonlesional TLE	Caucasian	*n* = 276 L/L = 77 (21.1) L/S = 146 (60.6) S/S = 53 (18.3)	*n* = 309 L/L = 90 (29.1) L/S = 142 (46.0) S/S = 77 (24.9)	NS

Table 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		*P* value
					Patients, *n* (%)	Controls, *n* (%)	
		Stefulj et al. 2010 [84]	TLE	Caucasian	*n* = 101 L/L = 42 (41.6) L/S = 45 (44.6) S/S = 14 (13.9)	*n* = 170 L/L = 60 (35.3) L/S = 93 (54.7) S/S = 17 (10.0)	NS
		Schenkel et al. 2011 [85]	TLE	Brazilian	*n* = 175 L/L = 48 (27.4) L/S = 91 (52.0) S/S = 36 (20.6)	*n* = 155 L/L = 54 (34.8) L/S = 64 (41.3) S/S = 37 (23.9)	NS
5-HTT	17 bp tandem repeat → intron 2 9, 10 and 12 repeats (rs71360731)	Manna et al. 2007 [83] Initial study	Nonlesional TLE	Caucasian	*n* = 276 12/12 = 126 (48.6) 12/10 = 112 (46.2) 10/10 = 38 (5.2)	*n* = 309 12/12 = 115 (37.2) 12/10 = 136 (44.0) 10/10 = 58 (18.8)	*0.0145*
		Kauffman et al. 2009 [86]	Response to treatment TLE-HS$^+$	Argentinean	Nonresponsive *n* = 74 12/12 = 40 (54.0) 12/10 = 23 (31.0) 10/10 = 10 (13.5) 12/9 = 1 (1.5) Responsive *n* = 31 12/12 = 7 (22.6) 12/10 = 21 (67.7) 10/10 = 3 (9.7) 12/9 = 0 (0.0)		Nonresponsive versus responsive =*0.006*
		Stefulj et al. 2010 [84]	TLE	Caucasian	*n* = 101 12/12 = 30 (30.9) 12/10 = 46 (47.4) 10/10 = 21 (21.6)	*n* = 170 12/12 = 64 (39.5) 12/10 = 74 (45.7) 10/10 = 24 (14.8)	NS
		Schenkel et al. 2011 [85]	TLE	Brazilian	*n* = 175 12/12 = 62 (35.4) 12/10 = 81 (46.3) 10/10 = 32 (18.3)	*n* = 155 12/12 = 67 (43.2) 12/10 = 67 (43.2) 10/10 = 21 (13.5)	NS
5-HT1B	c.861C>G → synonymous (rs6296)	Stefulj et al. 2010 [84]	TLE	Caucasian	*n* = 101 C/C = 2 (2.0) G/C = 35 (34.7) G/G = 64 (63.4)	*n* = 170 C/C = 14 (8.2) G/C = 65 (38.2) G/G = 91 (53.5)	*0.0642*
CALHM1	A>G → 3′UTR (rs11191692)	Lv et al. 2011 [87] Initial study	TLE	Chinese	*n* = 551 A/A = 50 (9.1) A/G = 257 (46.6) G/G = 244 (44.3)	*n* = 399 A/A = 30 (7.5) A/G = 149 (37.3) G/G = 220 (55.1)	*0.004*
		Lv et al. 2011 [87] Replication study	TLE	Chinese	*n* = 360 A/A = 34 (9.4) A/G = 168 (46.7) G/G = 158 (43.9)	*n* = 300 A/A = 20 (6.8) A/G = 111 (37.0) G/G = 169 (56.2)	*0.006*

n: number of individuals; TLE: temporal lobe epilepsy; NS: nonsignificant; TLE-FS$^{+/-}$: temporal lobe epilepsy with/without personal history of febrile seizures; TLE-HS$^{+/-}$: temporal lobe epilepsy with/without hippocampal sclerosis; ε4$^{+/-}$: ε4 present or not; significant P-values are in italic.

not observed in six other ethnically different populations [5, 67, 75, 77–79]. No association was found for *IL-1β*+3953 [67, 75, 76].

4.8. Prion Protein (PRNP). Cellular PRNP is a cellmembrane glycoprotein which is highly expressed in neurons in adults [95]. Two *PRNP* variants, p.Asn171Ser and p.Met129Val, have been studied in TLE patients. A first study found that p.Asn171Ser is associated with the seizure persisting after temporal lobectomy in TLE-HS$^+$ patients [80]. A replication study did not show this association in their unrelated patients [5]. Cognitive performance associated with the two *PRNP* variants was assessed in patients with medically refractory TLE-HS$^+$, as mentioned above [80]. These experiments showed no significant results [96]. However, recently, valine at codon 129 was shown to be highly represented in women with benign TLE as compared to the matched controls [81]. A Chinese study did not observe this difference in its TLE group [82].

4.9. Serotonin Transporter (5-HTT). 5-HTT is a key regulator of the level of serotoninergic neurotransmission through serotonin inactivation [97]. Moreover, 5-HTT is a target for selective serotonin reuptake inhibitors which have an anticonvulsant action [98]. The effect of two well-known functional polymorphisms of *5-HTT*, 5-HTTLPR (an insertion/deletion in 5′UTR) and 5-HTTVNTR (a VNTR in intron 2) was estimated in different TLE cohorts. Ten repeats at 5-HTTVNTR showed significantly lower frequencies in TLE than in controls, but no differences were displayed for 5-HTTLPR [83]. Subsequent studies showed that TLE-HS$^+$ patients carrying homozygous 5-HTTVNTR 12 repeats had an increased risk of not responding to medical treatment [86]. A particular genotype combination of 5-HTTLPR and 5-HTTVNTR (L/L-12/12) was associated with a worse response to optimal drug therapy in TLE patients [99]. Interestingly, this particular combination was significantly less frequently observed in another group of TLE patients than in the matched controls [85]. A recent study, which investigated several 5-HTT-related genes in Croatian TLE patients, did not show any association with the two functional polymorphisms of *5-HTT* but exhibited a significant allelic difference for *5-HT-1B* G861C. G-allele was slightly overrepresented in the TLE group [84].

4.10. Complement (C3). Complement factor C3 is a major component of the immune complement system. Experimental evidences have shown that this system plays a role in epileptic processes [100]. Moreover, increased expression of C3 gene and protein has been found in brain tissues from patients with mesial TLE (mTLE) [101, 102]. A dinucleotide repeat polymorphism (GF100472) located in the *C3* promoter and included in four particular haplotypes of 3 markers made by a combination of 5 SNPs (rs339392, rs2230199, rs428453, rs344550, rs379527) showed significant association even after the Bonferroni correction in TLE-FS$^+$. Replication in a second similar independent group confirmed one of the four haplotypes to be protective against TLE with a personal history of FS. This most significant protective haplotype in the initial and the replicative groups of TLE-FS$^+$ was (CA8)-G-T (GF100472- rs344550- rs379527) with a frequency of 0.025 and 0.022 in the control groups and 0.0 in the two patient groups ($P = 0.0003$ and $P = 0.00008$, resp.). Moreover, reporter gene assays confirmed that GF100472 significantly influenced *C3* promoter activity [103]. Up to now, no replicated association study has been assessed in another independent sample of TLE patients.

4.11. Calcium Homeostasis Modulator 1 (CALHM1). CALHM1 influences calcium (Ca^{2+}) homeostasis, which plays an important role in the development and maintenance of epilepsy [104]. Five SNPs (rs11191692, rs729211, rs2986016, rs2986018 and rs2986017) of *CALHM1* were genotyped in a Chinese population with TLE. Only one positive association was found between rs11191692, located in 3′UTR of the gene, and TLE patients [87]. As for the last one association study, no replication has yet been performed.

4.12. Lack of Association Results. Some studies found different genes to be of interest in TLE patients. A four-base insertion 12 bp before exon 2 in *sodium/potassium-transporting ATPase alpha 2 subunit* (*ATP1A2*) did not show any association between DNA from TLE anterior lobectomy tissue samples (15 TLE patients with 4bp insertion among 56 patients) and DNA from control blood samples (16 controls with 4bp insertion among 56 controls) [105]. Two SNPs (C271T and Val66Met), often associated with neurological conditions, in *brain-derived neurotrophic factor* (*BDNF*) were not associated with TLE in a European sample ($n = 151$) as compared to the matched controls ($n = 189$) [106]. A last negative result was obtained for *matrix metalloproteinase 9* gene (*MMP-9*) and TLE. In this experiment, 17 SNPs along *MMP-9* were tested and neither single SNP analysis nor haplotype analysis detected the *MMP-9* implication in 218 Norwegian TLE patients [107]. Today, association studies have been enlarged to genomewide association study (GWAS) in large cohort of patients. This strategy appears to be a method of choice for discovering SNPs or loci associated to numerous complex diseases [108]. The first GWAS in epilepsy field was recently achieved in 3445 patients showing partial epilepsy compared to 6935 matched controls [109]. This study did not find genomewide significant association. This was probably due to the important heterogeneity of the case sample. Unfortunately, the authors did not consider analysis in more homogeneous subsamples, such as TLE subgroup, that accounted for 919 patients with HS. They also did not make any effort to obtain a more homogenous sample of patients [109].

5. Conclusion

The main conclusion of the present paper is that the involvement of *LGI1* gene in familial ADLTE is the only replicated result in the field of the genetics of TLE. Several reasons could explain this lack of replication. First, this may be due to the small sample size of the TLE patients and/or

to the clinical heterogeneity in nearly all of the studies. Another reason is that gene-environment interaction has never been taken into account in the published studies, while this is likely to be an important etiological factor in such complex diseases. In connection with that is the absence of epigenetic studies in TLE (see below). Finally, TLE may also be caused by multiple rare mutations. This hypothesis is supported by the very recent mutations we identified in the *Carboxypeptidase A6* gene in a family as well as in sporadic TLE patients [110].

5.1. Future Directions. GWAS will require large and homogenous samples of TLE that will certainly be possible through international collaborations. Despite the complexity of such studies GWAS must be emphasized since the common—variant—common—disease has not yet be definitively rejected in TLE. In addition, high-throughput sequencing (HTS) of the whole genome or of the exome, the coding part of the genome, is the new way to consider this problem [111, 112]. To date, such HTS has not still been done in TLE. This was partially performed in a recent exome sequencing of ion channel genes in patients with idiopathic and symptomatic (formerly known as cryptogenic) epilepsy [113]. The study suggests that the phenotypic variation could occur because of many different channel alleles at a single locus or a collection of novel alleles in related or distant subunit genes [113]. Another type of rare polymorphisms to consider is structural variants such as copy number variations (CNVs) [114]. A recent genomewide CNVs study in various idiopathic, nonlesional epilepsies reported several rare CNVs in patients exhibiting generalized and focal epilepsies [115]. Although numerous efforts have been made to find a large number of causal genetic variations in complex diseases, there has been a growing interest for epigenetic variations, such as DNA methylation in complex human disease [116]. After a careful literature search, we only found one DNA methylation study on hippocampal subregions from mesial temporal sclerosis in patients with TLE. Results showed a greater level of reelin promoter methylation in TLE hippocampal dissections than in the controls [117]. Transcript levels of reelin, which is an extracellular matrix protein playing a role in the hippocampus cortical lamination, have been found downregulated in TLE specimens [117]. Epigenetic studies in the field of epilepsy are just at the starting point. Therefore, there are many avenues to understand how nongenetic components can act on the development of TLE. By combining these different approaches, we will be able to better understand the etiology of TLE. By doing so, we hope to provide personalized treatment to patients with complex disease, such as TLE.

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