

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 (*LGII*) gene, which has a putative role in development [11]. Kalachikov and colleagues were the first to describe 5 *LGII* mutations in five ADLTE families with auditory features (Table 1) [11]. After these initial results, numerous different *LGII* mutations have been linked to ADLTE (Table 1). Interestingly, 50% of ADLTE families did not show any *LGII* mutations [12]. Moreover, *de novo* *LGII* 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 *LGII* 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
<i>LGII</i>	c.1639insA	Frameshift, protein truncation	CI020606	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.611delC (835delC)	Frameshift, protein truncation	CD020573	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.136-3C>A (359-3C>A)	Intron retention, protein truncation	CM022035	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.1050-1051delCA	Frameshift, protein truncation	CD020574	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.1148A>C	p.Glu383Ala	rs28937874	ADLTE/ADPEAF	Kalachikov et al. 2002 [11]
<i>LGII</i>	c.758delC	Frameshift, protein truncation	CD021020	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16]
<i>LGII</i>	c.1420C>T	Premature stop codon, protein truncation	CM020950	ADLTE/ADPEAF	Morante-Redolat et al. 2002 [16] Bisulli et al. 2004 [13]
<i>LGII</i>	c.136T>C	p.Cys46Arg	rs104894166	ADLTE/ADPEAF	Gu et al. 2002 [17]
<i>LGII</i>	c.953T>G	p.Phe318Cys	rs28939075	ADLTE/ADPEAF	Fertig et al. 2003 [18]
<i>LGII</i>	c.598T>C	p.Cys200Arg	CM034239	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
<i>LGII</i>	c.1295T>A	p.Val432Glu	CM034240	ADLTE/ADPEAF	Michelucci et al. 2003 [19]
<i>LGII</i>	Unknown	p.Leu26Arg	Unknown	ADLTE/ADPEAF	Pizzuti et al. 2003 [20]
<i>LGII</i>	c.839-2A>C	Intron retention, protein truncation	Unknown	ADLTE/ADPEAF	Kobayashi et al. 2003 [21]
<i>LGII</i>	c.124T>G	p.Cys42Gly	CM041029	ADLTE/ADPEAF	Berkovic et al. 2004 [22]
<i>LGII</i>	c.1418C>T	p.Ser473Leu	CM041033	ADLTE/ADPEAF	Berkovic et al. 2004 [22] Kawamata et al. 2010 [23]
<i>LGII</i>	c.124T>C (348T>C)	p.Cys42Arg	CM041030	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.893T>C	p.Ile298Thr	CM041032	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.329C>A	p.Ala110Asp	CD044789	ADLTE/ADPEAF	Ottman et al. 2004 [24]
<i>LGII</i>	c.329delC	Frameshift, protein truncation	CD044789	ADLTE/ADPEAF	Hedera et al. 2004 [25]
<i>LGII</i>	c.435C>G	p.Ser145Arg	CM044660	ADLTE/ADPEAF	Hedera et al. 2004 [25]
<i>LGII</i>	c.461T>C	p.Leu154Pro	CM055408	ADLTE/ADPEAF	Pisano et al. 2005 [26]
<i>LGII</i>	c.406C>T	p.Arg136Trp	rs119488099	ADLTE/ADPEAF	Michelucci et al. 2007 [14]
<i>LGII</i>	c.431+1G>A	Deletion, protein truncation	Unknown	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
<i>LGII</i>	c.695T>C	p.Leu232Pro	rs104894167	ADLTE/ADPEAF	Chabrol et al. 2007 [27]
<i>LGII</i>	c.365T>A	p.Ile122Lys	rs119488100	ADLTE/ADPEAF	Striano et al. 2008 [28]
<i>LGII</i>	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
<i>LGII</i>	c.1421G>A	p.Arg474Glu	CM020950	ADLTE/ADPEAF	Kawamata et al. 2010 [23]
<i>LGII</i>	c.1219C>T	p.Arg407Cys	Unknown	ADLTE/ADPEAF	Striano et al. 2011 [30]
<i>SCN1A</i>	c.3809A>C	p.Lys1270Thr	rs121918626	TLE + GEFS ⁺	Abou-Khalil et al. 2001 [31]
<i>SCN1B</i>	c.363C>G	p.Cys121Trp	rs104894718	TLE + GEFS ⁺	Scheffer et al. 2007 [32]
<i>SCN1B</i>	Unknown	p.Arg85Cys	CM071081	TLE + GEFS ⁺	Scheffer et al. 2007 [32]
<i>SCN1B</i>	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 widely 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: $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. In a first association study, the $\epsilon 4$ 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* $\epsilon 4$ isoform. A study evaluating the memory in cases of mild, well-controlled nonlesional TLE found that $\epsilon 4$ 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 $\epsilon 4$ allele ($P < 0.01$) [91]. Two additional studies evaluated the relationship between the *ApoE* $\epsilon 4$ allele and postictal confusion in medically intractable TLE. Results were inconsistent. Chapin and colleagues found an association (68% of $\epsilon 4^+$ and 43% of $\epsilon 4^-$, $P = 0.04$) [92], whereas Kauffman and coworkers did not (30.4% of $\epsilon 4^+$ and 46.3% of $\epsilon 4^-$, $P = 0.2$) [93]. A final study investigated if *ApoE* $\epsilon 4$ 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 $\epsilon 4$ allele in their TLE patients only (20.7% of $\epsilon 4^+$ and 12.1% of $\epsilon 4^-$, $P = 0.023$) [94].

4.5. Interleukin 1 α (*IL-1 α*). *IL-1 α* is a major proinflammatory cytokine, which is synthesized during infection and inflammatory processes [90]. A single nucleotide polymorphism (SNP) on *IL-1 α* 5'UTR (*IL-1 α* -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-1 α* [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 1 β (*IL-1 β*). *IL-1 β* is another major proinflammatory cytokine and acts on the same IL-1 receptor as *IL-1 α* [74]. Two SNPs (*IL-1 β* -511 and *IL-1 β* +3953) were studied by Kanemoto and colleagues in TLE-HS^{+/−} patients. For *IL-1 β* -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 with sporadic TLE cases.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
GABBR1	c.1465G>A → p.Gly489Ser (CM031183)	Gambardella et al. 2003 [56]	Nonlesional TLE	Caucasian	n = 141	A/A = 0 (0.0) A/G = 24 (17.0) G/G = 117 (83.0)	n = 372	<0.0001
		Initial study				A/A = 0 (0.0) A/G = 2 (0.5) G/G = 370 (99.5)		
		Cavalleri et al. 2005 [5]	Nonlesional TLE	Caucasian	n = 245	A/A = 0 (0.0) A/G = 2 (1.0) G/G = 218 (99.0)	n = 1089	NS
		Replication study				A/A = 0 (0.0) A/G = 8 (1.0) G/G = 1062 (99.0)		
		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	NS
		Replication study				A/A = 1 (0.85) A/G = 0 (0.0) G/G = 117 (99.15)		
		Salzmann et al. 2005 [58]	Nonlesional TLE	Caucasian	n = 110	A/A = (0.0) A/G = 2 (1.82) G/G = 108 (98.18)	n = 145	NS
		Replication study				A/A = (0.0) A/G = (0.0) G/G = 145 (100)		
		Tan et al. 2005 [59]	Nonlesional TLE	Caucasian	n = 234	A/A = (0.0) A/G = 1 (0.4) G/G = 233 (99.6)	n = 164	NS
		Replication study				A/A = (0.0) A/G = 1 (0.6) G/G = 163 (99.4)		
Stögmänn et al. 2006 [60]	TLE	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
Wang et al. 2008 [62]	TLE	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

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Genomic variation counts		P value
					Patients, n (%)	Controls, n (%)	
<i>GABBR2</i>	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
<i>PDYN</i>	68 bp tandem repeat → promoter H-allele = 3 or 4 repeats L-allele = 1 or 2 repeats (rs71193945)	Stögmänn et al. 2002 [64] Initial study Gambardella et al. 2003 [65] Replication study Tilgen et al. 2003 [66] Replication study Cavalleri et al. 2005 [5] Replication study Salzmann et al. 2008 [67] Replication study Kauffman et al. 2008 [68]	Nonlesional TLE, familial risk Nonlesional TLE, familial risk Nonlesional TLE, familial risk Nonlesional TLE, familial risk Nonlesional TLE, familial risk	Caucasian Caucasian Caucasian Caucasian Argentinean	n = 43 L/L = 10 (23.3) L/H = 23 (53.5) H/H = 10 (23.3) n = 115 L/L = 9 (7.8) L/H = 40 (34.8) H/H = 66 (57.4) n = 46 L/L = 3 (7.0) L/H = 21 (45.0) H/H = 22 (48.0) n = 50 L/L = 8 (17.0) L/H = 22 (47.0) H/H = 17 (36.0) n = 21 L/L = 2 (9.5) L/H = 11 (52.4) H/H = 8 (38.1) n = 18 L/L = 1 (5.5) L/H = 8 (44.5) H/H = 9 (50.0)	n = 202 L/L = 18 (8.9) L/H = 88 (43.6) H/H = 96 (47.5) n = 259 L/L = 16 (6.2) L/H = 105 (40.5) H/H = 138 (53.3) n = 205 L/L = 22 (11.0) L/H = 84 (41.0) H/H = 99 (48.0) n = 384 L/L = 30 (8.0) L/H = 160 (44.0) H/H = 175 (48.0) n = 206 L/L = 14 (6.8) L/H = 78 (37.9) H/H = 114 (55.3) n = 86 L/L = 8 (9.3) L/H = 37 (43.0) H/H = 41 (47.7)	0.005 NS NS NS NS NS
<i>ApoE</i>	Isoform ε4 (CI056481)	Gambardella et al. 1999 [69] Initial study	Nonlesional TLE	Caucasian	n = 63 ε4 ⁺ = 5; years not indicated ε4 ⁻ = 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 $\epsilon 4$	Caucasian	n = 43 $\epsilon 4^+ = 10$; 5 \pm 5 years $\epsilon 4^- = 33$; 10 \pm 15 years		0.004
		Cavalleri et al. 2005 [5] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 181 $\epsilon 4^+ = 30$; 13.7 \pm 10 years $\epsilon 4^- =$ 151; 16.7 \pm 11 years n = 13 $\epsilon 4^+ = 24$; 26.2 \pm 20.1 years $\epsilon 4^- = 114$; 33.9 \pm 20.7 years		NS
		Gambardella et al. 2005 [71] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 47 $\epsilon 4^+ = 8$; 7.44 \pm 6.13 years $\epsilon 4^- = 39$; 8.75 \pm 7.61 years		NS
		Yeni et al. 2005 [72]	Early onset of TLE-HS ⁺ associated with $\epsilon 4$	Turkish	n = 106 $\epsilon 4^+ = 26$; 10.54 \pm 6.36 years $\epsilon 4^- = 80$; 16.51 \pm 9.90 years		0.003
		Salzmann et al. 2008 [67] Replication study	Early onset of TLE associated with $\epsilon 4$	Caucasian	n = 78 $\epsilon 4^+ = 23$; 14.3 \pm 12.13 years $\epsilon 4^- = 55$; 16.5 \pm 12.54 years		NS
<i>IL-1α</i>	c.-889C>T \rightarrow promoter Allele 1 = C Allele 2 = T (unknown)	Kanemoto et al. 2000 [74] Initial study	TLE-HS ^{+/−} associated with $\epsilon 4$	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	Patients, n (%)	Genomic variation counts	P value
					TLE-HS ⁻	Controls, n (%)	TLE-HS ⁻ versus controls = NS
					n = 53		
					1/1 = 44 (83.0)		
					1/2 = 8 (15.1)		
					2/2 = 1 (1.9)		
					n = 47	n = 99	NS
		Ozkara et al. 2006 [75]	TLE-HS ⁺	Turkish	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)	
					TLE-FS ⁺		TLE-FS ⁺ versus TLE-FS ⁻ = NS
		Ozkara et al. 2006 [75]	TLE-FS ^{+/-}	Turkish	n = 28		
		Initial study			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)		
					TLE-HS ⁺	n = 235	TLE-HS ⁺ versus controls = 0.027
		Salzmann et al. 2008 [67]	TLE-HS ^{+/-}	Caucasian	n = 86	1/1 = 99 (42.1)	
					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 controls = NS
					n = 23		
					1/1 = 15 (65.2)		
					1/2 = 7 (30.4)		
					2/2 = 1 (4.4)		
					TLE-FS ⁻		TLE-FS ⁺ versus controls = 0.0078
			TLE-FS ⁻	Caucasian	n = 54		
					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	Patients, n (%)	Genomic variation counts	P value
<i>IL-1RA</i>	86 bp tandem repeat → intron 2 Allele 4 = 5 repeats Allele 1 = 4 repeats Allele 2 = 2 repeats Allele 3 = 3 repeats Allele 5 = 6 repeats (rs2234663)	Kanemoto et al. 2000 [74] Initial study	TLE-HS ^{+/-}	Japanese	TLE-HS ⁺	n = 112	TLE-HS ⁺ versus controls = NS
					n = 50	1/1 = 102 (91.9)	
					1/1 = 46 (92.0)	1/2 = 6 (5.4)	
					1/2 = 3 (6.0)	1/3 = 1 (0.9)	
					1/3 = 1 (2.0)	1/4 = 2 (1.8)	
					1/4 = 0 (0.0)		
					TLE-HS ⁻	n = 53	TLE-HS ⁻ versus controls = NS
					n = 52 (98.1)		
					1/2 = 1 (1.9)		
					1/3 = 0 (0.0)		
1/4 = 0 (0.0)							
<i>IL-1β</i>	c.-511C>T → promoter Allele 1 = C Allele 2 = T (rs1799916)	Kanemoto et al. 2000 [74] Initial study	TLE-HS ^{+/-}	Japanese	TLE-HS ⁺	n = 242	TLE-HS ⁺ versus controls = NS
					n = 86	1/1 = 128 (52.9)	
					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 ⁻	n = 23	TLE-HS ⁻ versus controls = 0.001
					n = 5	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)							
<i>IL-1β</i>	c.-511C>T → promoter Allele 1 = C Allele 2 = T (rs1799916)	Kanemoto et al. 2000 [74] Initial study	TLE-HS ^{+/-}	Japanese	TLE-HS ⁺	n = 112	TLE-HS ⁺ versus controls = 0.0085
					n = 50	1/1 = 31 (27.7)	
					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 ⁻	n = 53	TLE-HS ⁻ versus controls = NS
					n = 53		
					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	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
		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 1/1 = 12 (18.2) 1/2 = 24 (36.4) 2/2 = 30 (45.5) TLE-HS ⁻ n = 64 1/1 = 16 (25.0) 1/2 = 36 (56.3) 2/2 = 12 (18.7)	n = 163 1/1 = 44 (27.0) 1/2 = 82 (50.3) 2/2 = 37 (22.7)	TLE-HS ⁺ versus controls = 0.0028 TLE-HS ⁻ versus controls = NS	
		Heils et al. 2000 [77]	TLE-HS ⁺	Caucasian	n = 86 1/1 = 33 (38.0) 1/2 = 42 (49.0) 2/2 = 11 (13.0)	n = 133 1/1 = 57 (42.0) 1/2 = 60 (45.0) 2/2 = 16 (12.0)	NS	
		Buono et al. 2001 [78]	TLE-HS ⁺	Caucasian	n = 61 1/1 = 31 (50.8) 1/2 = 24 (39.3) 2/2 = 6 (9.8)	n = 119 1/1 = 44 (37.0) 1/2 = 68 (57.1) 2/2 = 7 (5.9)	NS	
		Jin et al. 2003 [79]	TLE-HS ^{+/-}	Chinese	TLE-HS ⁺ n = 67 1/1 = 16 (24.0) 1/2 = 32 (48.0) 2/2 = 19 (28.0) TLE-HS ⁻ n = 45 1/1 = 12 (27.0) 1/2 = 24 (53.0) 2/2 = 9 (20.0)	n = 115 1/1 = 26 (23.0) 1/2 = 62 (54.0) 2/2 = 27 (23.0)	TLE-HS ⁺ versus controls = NS TLE-HS ⁻ versus controls = NS	
		Cavalleri et al. 2005 [5]	TLE-HS ⁺	Caucasian	n = 141 1/1 = 59 (45.0) 1/2 = 57 (44.0) 2/2 = 15 (11.0)	n = 384 1/1 = 161 (44.0) 1/2 = 162 (45.0) 2/2 = 41 (11.0)	NS	
		Ozkara et al. 2006 [75]	TLE-HS ⁺	Turkish	n = 47 1/1 = 16 (34.0) 1/2 = 21 (44.6) 2/2 = 10 (21.2)	n = 99 1/1 = 41 (41.4) 1/2 = 41 (41.4) 2/2 = 17 (17.1)	NS	
		Ozkara et al. 2006 [75] Initial study	TLE-FS ^{+/-}	Turkish	TLE-FS ⁺ n = 28 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)	TLE-FS ⁺ versus TLE-FS ⁻ = NS		

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
		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) TLE-HS [−] n = 23 1/1 = 12 (52.2) 1/2 = 9 (39.1) 2/2 = 2 (8.7)	Controls, n (%) n = 227 1/1 = 99 (43.6) 1/2 = 108 (47.6) 2/2 = 20 (8.8)	TLE-HS ⁺ versus controls = NS TLE-HS [−] versus controls = NS
<i>IL-1β</i>	IL-1β + 3953 → exon 5	Kanemoto et al. 2000 [74]	TLE-HS ^{+/−}	Japanese	TLE-HS ⁺ n = 50 1/1 = 45 (90.0) 1/2 = 5 (10.0) 2/2 = 0 (0.0) TLE-HS [−] n = 53 1/1 = 49 (92.5) 1/2 = 3 (5.7) 2/2 = 1 (1.9)	n = 112 1/1 = 105 (93.8) 1/2 = 7 (6.3) 2/2 = 0 (0.0)	TLE-HS ⁺ versus controls = NS
	Allele 1 and allele 2 (CM040228)	Initial study					
		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]	TLE-FS ^{+/−}	Turkish	TLE-FS ⁺ n = 28 1/1 = 19 (67.8) 1/2 = 9 (32.1) 2/2 = 0 (0.0) TLE-FS [−] n = 19 1/1 = 12 (63.1) 1/2 = 7 (36.8) 2/2 = 0 (0.0)		TLE-FS ⁺ versus TLE-FS [−] = NS
		Initial study					

TABLE 2: Continued.

Gene	Variation (accession number)	Reference	Group or subgroup of patients	Population origin	Patients, n (%)	Genomic variation counts	P value
		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)	Controls, n (%) 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 = 150 Met/Met = 146 (97.33) Met/Val = 4 (2.67) Val/Val = 0 (0.0)	n = 141 Met/Met = 77 (54.6) Met/Val = 54 (38.3) Val/Val = 10 (7.1) n = 302 Met/Met = 302 (96.79) Met/Val = 10 (3.31) Val/Val = 0 (0.0)	0.021
		Wang et al. 2008 [82]	Women, nonlesional TLE	Chinese			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	Patients, n (%)	Genomic variation counts	Controls, n (%)	P value
5-HTT	17 bp tandem repeat → intron 2 9, 10 and 12 repeats (rs71360731)	Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	NS	
					L/L = 42 (41.6)	L/L = 60 (35.3)		
					L/S = 45 (44.6)	L/S = 93 (54.7)		
Schenkel et al. 2011 [85]	TLE	Brazilian	n = 175	n = 155	NS			
			L/L = 48 (27.4)	L/L = 54 (34.8)				
			L/S = 91 (52.0)	L/S = 64 (41.3)				
Manna et al. 2007 [83]	Nonlesional TLE	Caucasian	n = 276	n = 309	0.0145			
			12/12 = 126 (48.6)	12/12 = 115 (37.2)				
			12/10 = 112 (46.2)	12/10 = 136 (44.0)				
Kauffman et al. 2009 [86]	Response to treatment	Argentinean	Nonresponsive	10/10 = 58 (18.8)	Nonresponsive versus responsive = 0.006			
			n = 74					
			12/12 = 40 (54.0)					
Stefulj et al. 2010 [84]	TLE	Caucasian	Responsive	n = 170	NS			
			n = 31					
			12/12 = 7 (22.6)	12/12 = 64 (39.5)				
Schenkel et al. 2011 [85]	TLE	Brazilian	12/10 = 21 (67.7)	12/10 = 74 (45.7)	NS			
			10/10 = 3 (9.7)	10/10 = 24 (14.8)				
			12/9 = 0 (0.0)	n = 155				
Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	NS			
			12/12 = 30 (30.9)	12/12 = 67 (43.2)				
			12/10 = 46 (47.4)	12/10 = 67 (43.2)				
Schenkel et al. 2011 [85]	TLE	Brazilian	10/10 = 21 (21.6)	10/10 = 21 (13.5)	NS			
			n = 175	n = 155				
			12/12 = 62 (35.4)	12/12 = 67 (43.2)				
5-HTT	c.861C>G → synonymous (rs6296)	Stefulj et al. 2010 [84]	TLE	Caucasian	n = 101	n = 170	0.0642	
					C/C = 2 (2.0)	C/C = 14 (8.2)		
					G/C = 35 (34.7)	G/C = 65 (38.2)		
CALHM1	A>G → 3'UTR (rs11191692)	Lv et al. 2011 [87]	TLE	Chinese	n = 551	n = 399	0.004	
					A/A = 50 (9.1)	A/A = 30 (7.5)		
					A/G = 257 (46.6)	A/G = 149 (37.3)		
Lv et al. 2011 [87]	Replication study	Chinese	G/G = 244 (44.3)	G/G = 220 (55.1)	0.006			
			n = 360	n = 300				
			A/A = 34 (9.4)	A/A = 20 (6.8)				
Lv et al. 2011 [87]	Replication study	Chinese	A/G = 168 (46.7)	A/G = 111 (37.0)	0.006			
			G/G = 158 (43.9)	G/G = 169 (56.2)				

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; e4^{+/−}: e4 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-1 β* +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 serotonergic 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 (Ca²⁺) 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 *LGII* 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 homogeneous 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 been 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.

References

- [1] J. Roger, F. E. Dreifuss, M. Martinez-Lage et al., "Proposal for revised classification of epilepsies and epileptic syndromes," *Epilepsia*, vol. 30, no. 4, pp. 389–399, 1989.
- [2] V. Eisner, L. L. Pauli, and S. Livingston, "Hereditary aspects of epilepsy," *Bulletin of the Johns Hopkins Hospital*, vol. 105, pp. 245–271, 1959.
- [3] E. Andermann and J. D. Matrakos, "Proceedings: a multifactorial analysis of focal and generalized cortico-reticular (centrencephalic) epilepsy," *Epilepsia*, vol. 13, no. 2, pp. 348–349, 1972.
- [4] R. Ottman, "Genetics of the partial epilepsies: a review," *Epilepsia*, vol. 30, no. 1, pp. 107–111, 1989.
- [5] G. L. Cavalleri, J. M. Lynch, C. Depondt et al., "Failure to replicate previously reported genetic associations with sporadic temporal lobe epilepsy: where to from here?" *Brain*, vol. 128, no. 8, pp. 1832–1840, 2005.
- [6] R. Ottman, N. Risch, W. A. Hauser et al., "Localization of a gene for partial epilepsy to chromosome 10q," *Nature Genetics*, vol. 10, no. 1, pp. 56–60, 1995.
- [7] J. J. Poza, A. Sáenz, A. Martínez-Gil et al., "Autosomal dominant lateral temporal epilepsy: clinical and genetic study of a large Basque pedigree linked to chromosome 10q," *Annals of Neurology*, vol. 45, no. 2, pp. 182–188, 1999.
- [8] V. F. Mautner, M. Lindenau, A. Gottesleben, G. Goetze, and L. Kluwe, "Supporting evidence of a gene for partial epilepsy on 10q," *Neurogenetics*, vol. 3, no. 1, pp. 31–34, 2000.
- [9] M. R. Winawer, F. M. Boneschi, C. Barker-Cummings et al., "Four new families with autosomal dominant partial epilepsy with auditory features: clinical description and linkage to chromosome 10q24," *Epilepsia*, vol. 43, no. 1, pp. 60–67, 2002.
- [10] E. Brodtkorb, W. Gu, K. O. Nakken, C. Fischer, and O. K. Steinlein, "Familial temporal lobe epilepsy with aphasic seizures and linkage to chromosome 10q22–q24," *Epilepsia*, vol. 43, no. 3, pp. 228–235, 2002.
- [11] S. Kalachikov, O. Evgrafov, B. Ross et al., "Mutations in LGI1 cause autosomal-dominant partial epilepsy with auditory features," *Nature Genetics*, vol. 30, no. 3, pp. 335–341, 2002.
- [12] C. Nobile, R. Michelucci, S. Andreazza, E. Pasini, S. C. E. Tosatto, and P. Striano, "LGI1 mutations in autosomal dominant and sporadic lateral temporal epilepsy," *Human Mutation*, vol. 30, no. 4, pp. 530–536, 2009.
- [13] F. Bisulli, P. Tinuper, E. Scudellaro et al., "A de novo LGI1 mutation in sporadic partial epilepsy with auditory features," *Annals of Neurology*, vol. 56, no. 3, pp. 455–456, 2004.
- [14] R. Michelucci, O. Mecarelli, G. Bovo et al., "A de novo LGI1 mutation causing idiopathic partial epilepsy with telephone-induced seizures," *Neurology*, vol. 68, no. 24, pp. 2150–2151, 2007.
- [15] G. Bovo, E. Diani, F. Bisulli et al., "Analysis of LGI1 promoter sequence, PDYN and GABBR1 polymorphisms in sporadic and familial lateral temporal lobe epilepsy," *Neuroscience Letters*, vol. 436, no. 1, pp. 23–26, 2008.
- [16] J. M. Morante-Redolat, A. Gorostidi-Pagola, S. Piquer-Sirerol et al., "Mutations in the LGI1/Epitempin gene on 10q24 cause autosomal dominant lateral temporal epilepsy," *Human Molecular Genetics*, vol. 11, no. 9, pp. 1119–1128, 2002.
- [17] W. Gu, E. Brodtkorb, and O. K. Steinlein, "LGI1 is mutated in familial temporal lobe epilepsy characterized by aphasic seizures," *Annals of Neurology*, vol. 52, no. 3, pp. 364–367, 2002.
- [18] E. Fertig, A. Lincoln, A. Martinuzzi, R. H. Mattson, and F. M. Hisama, "Novel LGI1 mutation in a family with autosomal dominant partial epilepsy with auditory features," *Neurology*, vol. 60, no. 10, pp. 1687–1690, 2003.
- [19] R. Michelucci, J. J. Poza, V. Sofia et al., "Autosomal dominant lateral temporal epilepsy: clinical spectrum, new epitempin mutations, and genetic heterogeneity in seven European families," *Epilepsia*, vol. 44, no. 10, pp. 1289–1297, 2003.

- [20] A. Pizzuti, E. Flex, C. Di Bonaventura et al., "Epilepsy with auditory features: a LGI1 gene mutation suggests a loss-of-function mechanism," *Annals of Neurology*, vol. 53, no. 3, pp. 396–399, 2003.
- [21] E. Kobayashi, N. F. Santos, F. R. Torres et al., "Magnetic resonance imaging abnormalities in familial temporal lobe epilepsy with auditory auras," *Archives of Neurology*, vol. 60, no. 11, pp. 1546–1551, 2003.
- [22] S. F. Berkovic, P. Izzillo, J. M. McMahon et al., "LGI1 mutations in temporal lobe epilepsies," *Neurology*, vol. 62, no. 7, pp. 1115–1119, 2004.
- [23] J. Kawamata, A. Ikeda, Y. Fujita, K. Usui, S. Shimohama, and R. Takahashi, "Mutations in LGI1 gene in Japanese families with autosomal dominant lateral temporal lobe epilepsy: the first report from Asian families," *Epilepsia*, vol. 51, no. 4, pp. 690–693, 2010.
- [24] R. Ottman, M. R. Winawer, S. Kalachikov et al., "LGI1 mutations in autosomal dominant partial epilepsy with auditory features," *Neurology*, vol. 62, no. 7, pp. 1120–1126, 2004.
- [25] P. Hedera, B. Abou-Khalil, A. E. Crunk, K. A. Taylor, J. L. Haines, and J. S. Sutcliffe, "Autosomal dominant lateral temporal epilepsy: two families with novel mutations in the LGI1 gene," *Epilepsia*, vol. 45, no. 3, pp. 218–222, 2004.
- [26] T. Pisano, C. Marini, P. Brovedani et al., "Abnormal phonologic processing in familial lateral temporal lobe epilepsy due to a new LGI1 mutation," *Epilepsia*, vol. 46, no. 1, pp. 118–123, 2005.
- [27] E. Chabrol, C. Popescu, I. Gourfinkel-An et al., "Two novel epilepsy-linked mutations leading to a loss of function of LGI1," *Archives of Neurology*, vol. 64, no. 2, pp. 217–222, 2007.
- [28] P. Striano, A. de Falco, E. Diani et al., "A novel loss-of-function LGI1 mutation linked to autosomal dominant lateral temporal epilepsy," *Archives of Neurology*, vol. 65, no. 7, pp. 939–942, 2008.
- [29] C. D. Bonaventura, M. Carni, E. Diani et al., "Drug resistant ADLTE and recurrent partial status epilepticus with dysphasic features in a family with a novel LGI1 mutation: electroclinical, genetic, and EEG/fMRI findings," *Epilepsia*, vol. 50, no. 11, pp. 2481–2486, 2009.
- [30] P. Striano, G. Busolin, L. Santulli et al., "Familial temporal lobe epilepsy with psychic auras associated with a novel LGI1 mutation," *Neurology*, vol. 76, no. 13, pp. 1173–1176, 2011.
- [31] B. Abou-Khalil, Q. Ge, R. Desai et al., "Partial and generalized epilepsy with febrile seizures plus and a novel SCN1A mutation," *Neurology*, vol. 57, no. 12, pp. 2265–2272, 2001.
- [32] I. E. Scheffer, L. A. Harkin, B. E. Grinton et al., "Temporal lobe epilepsy and GEFS+ phenotypes associated with SCN1B mutations," *Brain*, vol. 130, no. 1, pp. 100–109, 2007.
- [33] S. F. Berkovic, A. McIntosh, R. Anne Howell, A. Mitchell, L. J. Sheffield, and J. L. Hopper, "Familial temporal lobe epilepsy: a common disorder identified in twins," *Annals of Neurology*, vol. 40, no. 2, pp. 227–235, 1996.
- [34] A. Gambardella, D. Messina, E. Le Piane et al., "Familial temporal lobe epilepsy—autosomal dominant inheritance in a large pedigree from Southern Italy," *Epilepsy Research*, vol. 38, no. 2–3, pp. 127–132, 2000.
- [35] P. Hedera, M. A. Blair, E. Andermann et al., "Familial mesial temporal lobe epilepsy maps to chromosome 4q13.2–q21.3," *Neurology*, vol. 68, no. 24, pp. 2107–2112, 2007.
- [36] M. A. Falconer, E. A. Serafetinides, and J. A. Corsellis, "Etiology and pathogenesis of temporal lobe epilepsy," *Archives of neurology*, vol. 10, pp. 233–248, 1964.
- [37] F. Cendes, F. Andermann, F. Dubeau et al., "Early childhood prolonged febrile convulsions, atrophy and sclerosis of mesial structures, and temporal lobe epilepsy: an MRI volumetric study," *Neurology*, vol. 43, no. 6, pp. 1083–1087, 1993.
- [38] J. B. M. Kuks, M. J. Cook, D. R. Fish, J. M. Stevens, and S. D. Shorvon, "Hippocampal sclerosis in epilepsy and childhood febrile seizures," *The Lancet*, vol. 342, no. 8884, pp. 1391–1394, 1993.
- [39] J. Maher and R. S. McLachlan, "Febrile convulsions: is seizure duration the most important predictor of temporal lobe epilepsy?" *Brain*, vol. 118, no. 6, pp. 1521–1528, 1995.
- [40] E. Kobayashi, I. Lopes-Cendes, C. A. M. Guerreiro, S. C. Sousa, M. M. Guerreiro, and F. Cendes, "Seizure outcome and hippocampal atrophy in familial mesial temporal lobe epilepsy," *Neurology*, vol. 56, no. 2, pp. 166–172, 2001.
- [41] B. Abou-Khalil, E. Andermann, F. Andermann, A. Olivier, and L. F. Quesney, "Temporal lobe epilepsy after prolonged febrile convulsions: excellent outcome after surgical treatment," *Epilepsia*, vol. 34, no. 5, pp. 878–883, 1993.
- [42] E. Kobayashi, L. M. Li, I. Lopes-Cendes, and F. Cendes, "Magnetic resonance imaging evidence of hippocampal sclerosis in asymptomatic, first-degree relatives of patients with familial mesial temporal lobe epilepsy," *Archives of Neurology*, vol. 59, no. 12, pp. 1891–1894, 2002.
- [43] F. Cendes, I. Lopes-Cendes, E. Andermann, and F. Andermann, "Familial temporal lobe epilepsy: a clinically heterogeneous syndrome," *Neurology*, vol. 50, no. 2, pp. 554–557, 1998.
- [44] I. E. Scheffer, Y. H. Zhang, F. E. Jansen, and L. Dibbens, "Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus?" *Brain and Development*, vol. 31, no. 5, pp. 394–400, 2009.
- [45] R. Singh, I. E. Scheffer, K. Crossland, and S. F. Berkovic, "Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome," *Annals of Neurology*, vol. 45, no. 1, pp. 75–81, 1999.
- [46] A. Escayg, B. T. MacDonald, M. H. Meisler et al., "Mutations of SCN1A, encoding a neuronal sodium channel, in two families with GEFS+2," *Nature Genetics*, vol. 24, no. 4, pp. 343–345, 2000.
- [47] R. H. Wallace, D. W. Wang, R. Singh et al., "Febrile seizures and generalized epilepsy associated with a mutation in the Na⁺-channel β 1 subunit gene SCN1B," *Nature Genetics*, vol. 19, no. 4, pp. 366–370, 1998.
- [48] S. Baulac, F. Picard, A. Herman et al., "Evidence for digenic inheritance in a family with both febrile convulsions and temporal lobe epilepsy implicating chromosomes 18qter and 1q25–q31," *Annals of Neurology*, vol. 49, no. 6, pp. 786–792, 2001.
- [49] R. Nabbout, S. Baulac, I. Desguerre et al., "New locus for febrile seizures with absence epilepsy on 3p and a possible modifier gene on 18p," *Neurology*, vol. 68, no. 17, pp. 1374–1381, 2007.
- [50] D. Angelicheva, I. Tournev, V. Guergueltcheva et al., "Partial epilepsy syndrome in a Gypsy family linked to 5q31.3–q32," *Epilepsia*, vol. 50, no. 7, pp. 1679–1688, 2009.
- [51] A. Sirén, A. Polvi, L. Chahine et al., "Suggestive evidence for a new locus for epilepsy with heterogeneous phenotypes on chromosome 17q," *Epilepsy Research*, vol. 88, no. 1, pp. 65–75, 2010.
- [52] C. Depondt, W. Van Paesschen, G. Matthijs et al., "Familial temporal lobe epilepsy with febrile seizures," *Neurology*, vol. 58, no. 9, pp. 1429–1433, 2002.

- [53] C. V. Maurer-Morelli, R. Secolin, R. B. Marchesini et al., "THE SCN2A gene is not a likely candidate for familial mesial temporal lobe epilepsy," *Epilepsy Research*, vol. 71, no. 2-3, pp. 233–236, 2006.
- [54] L. R. Cardon and J. I. Bell, "Association study designs for complex diseases," *Nature Reviews Genetics*, vol. 2, no. 2, pp. 91–99, 2001.
- [55] N. C. K. Tan, J. C. Mulley, and S. F. Berkovic, "Genetic association studies in epilepsy: "The truth is out there"," *Epilepsia*, vol. 45, no. 11, pp. 1429–1442, 2004.
- [56] A. Gambardella, I. Manna, A. Labate et al., "GABA(B) receptor 1 polymorphism (G1465A) is associated with temporal lobe epilepsy," *Neurology*, vol. 60, no. 4, pp. 560–563, 2003.
- [57] S. Ma, B. Abou-Khalil, J. S. Sutcliffe, J. L. Haines, and P. Hedera, "The GABBR1 locus and the G1465A variant is not associated with temporal lobe epilepsy preceded by febrile seizures," *BMC Medical Genetics*, vol. 6, article 13, 2005.
- [58] A. Salzmann, B. Moulard, A. Crespel, M. Baldy-Moulinier, C. Buresi, and A. Malafosse, "GABAB receptor 1 polymorphism (G1465A) and temporal lobe epilepsy," *Epilepsia*, vol. 46, no. 6, pp. 931–933, 2005.
- [59] N. C. K. Tan, S. E. Heron, I. E. Scheffer, S. F. Berkovic, and J. C. Mulley, "Is variation in the GABA(B) receptor 1 gene associated with temporal lobe epilepsy?" *Epilepsia*, vol. 46, no. 5, pp. 778–780, 2005.
- [60] E. Stogmann, A. Zimprich, C. Baumgartner, A. Gleiss, and F. Zimprich, "Lack of association between a GABAB receptor 1 gene polymorphism and temporal lobe epilepsy," *Epilepsia*, vol. 47, no. 2, pp. 437–439, 2006.
- [61] L. Ren, L. Jin, B. Zhang, Y. Jia, L. Wu, and Y. Shen, "Lack of GABABR1 gene variation (G1465A) in a Chinese population with temporal lobe epilepsy," *Seizure*, vol. 14, no. 8, pp. 611–613, 2005.
- [62] X. Wang, W. Sun, X. Zhu et al., "Association between the γ -aminobutyric acid type B receptor 1 and 2 gene polymorphisms and mesial temporal lobe epilepsy in a Han Chinese population," *Epilepsy Research*, vol. 81, no. 2-3, pp. 198–203, 2008.
- [63] M. A. Kauffman, E. M. Levy, D. Consalvo, J. Mordoh, and S. Kochen, "GABABR1 (G1465A) gene variation and temporal lobe epilepsy controversy: new evidence," *Seizure*, vol. 17, no. 6, pp. 567–571, 2008.
- [64] E. Stögmann, A. Zimprich, C. Baumgartner, S. Aull-Watschinger, V. Höllt, and F. Zimprich, "A functional polymorphism in the prodynorphin gene promoter is associated with temporal lobe epilepsy," *Annals of Neurology*, vol. 51, no. 2, pp. 260–263, 2002.
- [65] A. Gambardella, I. Manna, A. Labate et al., "Prodynorphin gene promoter polymorphism and temporal lobe epilepsy," *Epilepsia*, vol. 44, no. 9, pp. 1255–1256, 2003.
- [66] N. Tilgen, J. Rebstock, S. Horvath et al., "Prodynorphin gene promoter polymorphism and temporal lobe epilepsy," *Annals of Neurology*, vol. 53, no. 2, pp. 280–282, 2003.
- [67] A. Salzmann, N. Perroud, A. Crespel, C. Lamercy, and A. Malafosse, "Candidate genes for temporal lobe epilepsy: a replication study," *Neurological Sciences*, vol. 29, no. 6, pp. 397–403, 2008.
- [68] M. A. Kauffman, D. Consalvo, M. D. Gonzalez, and S. Kochen, "Transcriptionally less active prodynorphin promoter alleles are associated with Temporal Lobe Epilepsy: a case-control study and meta-analysis," *Disease Markers*, vol. 24, no. 3, pp. 135–140, 2008.
- [69] A. Gambardella, U. Aguglia, R. Cittadella et al., "Apolipoprotein E polymorphisms and the risk of nonlesional temporal lobe epilepsy," *Epilepsia*, vol. 40, no. 12, pp. 1804–1807, 1999.
- [70] R. S. Briellmann, Y. Torn-Broers, B. E. Busuttill et al., "APOE ϵ 4 genotype is associated with an earlier onset of chronic temporal lobe epilepsy," *Neurology*, vol. 55, no. 3, pp. 435–437, 2000.
- [71] A. Gambardella, U. Aguglia, R. Chifari et al., "ApoE epsilon4 allele and disease duration affect verbal learning in mild temporal lobe epilepsy," *Epilepsia*, vol. 46, no. 1, pp. 110–117, 2005.
- [72] S. N. Yeni, Ç. Özkara, N. Buyru et al., "Association between APOE polymorphisms and mesial temporal lobe epilepsy with hippocampal sclerosis," *European Journal of Neurology*, vol. 12, no. 2, pp. 103–107, 2005.
- [73] M. A. Kauffman, D. Consalvo, D. G. Moron, V. P. Lereis, and S. Kochen, "ApoE epsilon4 genotype and the age at onset of temporal lobe epilepsy: a case-control study and meta-analysis," *Epilepsy Research*, vol. 90, no. 3, pp. 234–239, 2010.
- [74] K. Kanemoto, J. Kawasaki, T. Miyamoto, H. Obayashi, and M. Nishimura, "Interleukin (IL)-1 β , IL-1 α , and IL-1 receptor antagonist gene polymorphisms in patients with temporal lobe epilepsy," *Annals of Neurology*, vol. 47, no. 5, pp. 571–574, 2000.
- [75] C. Ozkara, M. Uzan, T. Tanriverdi et al., "Lack of association between IL-1 β / α gene polymorphisms and temporal lobe epilepsy with hippocampal sclerosis," *Seizure*, vol. 15, no. 5, pp. 288–291, 2006.
- [76] K. Kanemoto, J. Kawasaki, S. Yuasa et al., "Increased frequency of interleukin-1 β -511T allele in patients with temporal lobe epilepsy, hippocampal sclerosis, and prolonged febrile convulsion," *Epilepsia*, vol. 44, no. 6, pp. 796–799, 2003.
- [77] A. Heils, K. Haug, W. S. Kunz et al., "Interleukin-1 β gene polymorphism and susceptibility to temporal lobe epilepsy with hippocampal sclerosis [2] (multiple letters)," *Annals of Neurology*, vol. 48, no. 6, pp. 948–950, 2000.
- [78] R. J. Buono, T. N. Ferraro, M. J. O'Connor et al., "Lack of association between an interleukin 1 beta (IL-1 β) gene variation and refractory temporal lobe epilepsy," *Epilepsia*, vol. 42, no. 6, pp. 782–784, 2001.
- [79] L. Jin, Y. Jia, B. Zhang et al., "Association analysis of a polymorphism of interleukin 1 β (IL-1 β) gene with temporal lobe epilepsy in a Chinese population," *Epilepsia*, vol. 44, no. 10, pp. 1306–1309, 2003.
- [80] R. Walz, R. M. R. P. S. Castro, T. R. Velasco et al., "Surgical outcome in mesial temporal sclerosis correlates with prion protein gene variant," *Neurology*, vol. 61, no. 9, pp. 1204–1210, 2003.
- [81] A. Labate, I. Manna, A. Gambardella et al., "Association between the M129V variant allele of PRNP gene and mild temporal lobe epilepsy in women," *Neuroscience Letters*, vol. 421, no. 1, pp. 1–4, 2007.
- [82] X. Wang, W. Sun, X. Zhu et al., "M129V polymorphism in the prion protein gene is not associated with mesial temporal lobe epilepsy in a Han Chinese population," *European Journal of Neurology*, vol. 15, no. 8, pp. 827–830, 2008.
- [83] I. Manna, A. Labate, A. Gambardella et al., "Serotonin transporter gene (5-Htt): association analysis with temporal lobe epilepsy," *Neuroscience Letters*, vol. 421, no. 1, pp. 52–56, 2007.
- [84] J. Stefulj, T. Bordukalo-Niksic, H. Hecimovic, V. Demarin, and B. Jernej, "Epilepsy and serotonin (5HT): variations of

- 5HT-related genes in temporal lobe epilepsy,” *Neuroscience Letters*, vol. 478, no. 1, pp. 29–31, 2010.
- [85] L. C. Schenkel, J. A. Bragatti, C. M. Torres et al., “Serotonin transporter gene (5HTT) polymorphisms and temporal lobe epilepsy,” *Epilepsy Research*, vol. 95, no. 1-2, pp. 152–157, 2011.
- [86] M. A. Kauffman, D. Consalvo, D. Gonzalez-Morón, F. Aguirre, L. D’Alessio, and S. Kochen, “Serotonin transporter gene variation and refractory mesial temporal epilepsy with hippocampal sclerosis,” *Epilepsy Research*, vol. 85, no. 2-3, pp. 231–234, 2009.
- [87] R. J. Lv, J. S. He, Y. H. Fu et al., “A polymorphism in CALHM1 is associated with temporal lobe epilepsy,” *Epilepsy and Behavior*, vol. 20, no. 4, pp. 681–685, 2011.
- [88] A. Billinton, V. H. Baird, M. Thom, J. S. Duncan, N. Upton, and N. G. Bowery, “GABAB(1) mRNA expression in hippocampal sclerosis associated with human temporal lobe epilepsy,” *Molecular Brain Research*, vol. 86, no. 1-2, pp. 84–89, 2001.
- [89] A. Zimprich, J. Kraus, M. Wöltje, P. Mayer, E. Rauch, and V. Höllt, “An allelic variation in the human prodynorphin gene promoter alters stimulus-induced expression,” *Journal of Neurochemistry*, vol. 74, no. 2, pp. 472–477, 2000.
- [90] P. R. Wenham, C. R. Newton, and W. H. Price, “Analysis of apolipoprotein E genotypes by the amplification refractory mutation system,” *Clinical Chemistry*, vol. 37, no. 2, pp. 241–244, 1991.
- [91] R. M. Busch, T. T. Lineweaver, R. I. Naugle et al., “ApoE- ϵ 4 is associated with reduced memory in long-standing intractable temporal lobe epilepsy,” *Neurology*, vol. 68, no. 6, pp. 409–414, 2007.
- [92] J. S. Chapin, R. M. Busch, D. Janigro et al., “APOE ϵ 4 is associated with postictal confusion in patients with medically refractory temporal lobe epilepsy,” *Epilepsy Research*, vol. 81, no. 2-3, pp. 220–224, 2008.
- [93] M. A. Kauffman, N. Pereira-de-Silva, D. Consalvo, and S. Kochen, “ApoE ϵ 4 is not associated with postictal confusion in patients with mesial temporal lobe epilepsy with hippocampal sclerosis,” *Epilepsy Research*, vol. 85, no. 2-3, pp. 311–313, 2009.
- [94] Y. H. Fu, R. J. Lv, L. R. Jin et al., “Association of apolipoprotein E polymorphisms with temporal lobe epilepsy in a Chinese Han population,” *Epilepsy Research*, vol. 91, no. 2-3, pp. 253–259, 2010.
- [95] S. B. Prusiner, “Prions,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 95, no. 23, pp. 13363–13383, 1998.
- [96] E. R. Coimbra, K. Rezek, S. Escorsi-Rosset et al., “Cognitive performance of patients with mesial temporal lobe epilepsy is not associated with human prion protein gene variant allele at codons 129 and 171,” *Epilepsy and Behavior*, vol. 8, no. 3, pp. 635–642, 2006.
- [97] K. P. Lesch and R. Mössner, “Genetically driven variation in serotonin uptake: is there a link to affective spectrum, neurodevelopmental, and neurodegenerative disorders?” *Biological Psychiatry*, vol. 44, no. 3, pp. 179–192, 1998.
- [98] E. Favale, D. Audenino, L. Cocito, and C. Albano, “The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis,” *Seizure*, vol. 12, no. 5, pp. 316–318, 2003.
- [99] H. Hecimovic, S. Jasminka, C. S. Lipa, D. Vida, and J. Branimir, “Association of serotonin transporter promoter (5-HTTLPR) and intron 2 (VNTR-2) polymorphisms with treatment response in temporal lobe epilepsy,” *Epilepsy Research*, vol. 91, no. 1, pp. 35–38, 2010.
- [100] Z. Q. Xiong, W. Qian, K. Suzuki, and J. O. McNamara, “Formation of complement membrane attack complex in mammalian cerebral cortex evokes seizures and neurodegeneration,” *Journal of Neuroscience*, vol. 23, no. 3, pp. 955–960, 2003.
- [101] S. Jamali, F. Bartolomei, A. Robaglia-Schlupp et al., “Large-scale expression study of human mesial temporal lobe epilepsy: evidence for dysregulation of the neurotransmission and complement systems in the entorhinal cortex,” *Brain*, vol. 129, no. 3, pp. 625–641, 2006.
- [102] E. Aronica, K. Boer, E. A. van Vliet et al., “Complement activation in experimental and human temporal lobe epilepsy,” *Neurobiology of Disease*, vol. 26, no. 3, pp. 497–511, 2007.
- [103] S. Jamali, A. Salzmänn, N. Perroud et al., “Functional variant in complement C3 gene promoter and genetic susceptibility to temporal lobe epilepsy and febrile seizures,” *PLoS ONE*, vol. 5, no. 9, Article ID 12740, pp. 1–8, 2010.
- [104] R. J. DeLorenzo, D. A. Sun, and L. S. Deshpande, “Cellular mechanisms underlying acquired epilepsy: the calcium hypothesis of the induction and maintenance of epilepsy,” *Pharmacology and Therapeutics*, vol. 105, no. 3, pp. 229–266, 2005.
- [105] R. J. Bueno, T. N. Ferraro, M. J. O’Connor et al., “Lack of association between temporal lobe epilepsy and a novel polymorphism in the alpha 2 subunit gene (ATP21A2) of the sodium potassium transporting ATPase,” *American Journal of Medical Genetics*, vol. 96, no. 1, pp. 79–83, 2000.
- [106] F. W. Lohoff, T. N. Ferraro, J. P. Dahl et al., “Lack of association between variations in the brain-derived neurotrophic factor (BDNF) gene and temporal lobe epilepsy,” *Epilepsy Research*, vol. 66, no. 1–3, pp. 59–62, 2005.
- [107] K. Heuser, E. H. Hoddevik, E. Taubøll et al., “Temporal Lobe Epilepsy and Matrix Metalloproteinase 9: a tempting relation but negative genetic association,” *Seizure*, vol. 19, no. 6, pp. 335–338, 2010.
- [108] H. Hakonarson and S. F.A. Grant, “Planning a genome-wide association study: points to consider,” *Annals of Medicine*, vol. 43, no. 6, pp. 451–460, 2011.
- [109] D. Kasperaviciute, C. B. Catarino, E. L. Heinzen et al., “Common genetic variation and susceptibility to partial epilepsies: a genome-wide association study,” *Brain*, vol. 133, no. 7, pp. 2136–2147, 2010.
- [110] A. Salzmänn, M. Guipponi, P. J. Lyons et al., “Carboxypeptidase A6 gene (CPA6) mutations in a recessive familial form of febrile seizures and temporal lobe epilepsy and in sporadic temporal lobe epilepsy,” *Human Mutation*. In press.
- [111] J. Majewski, J. Schwartzentruber, E. Lalonde, A. Montpetit, and N. Jabado, “What can exome sequencing do for you?” *Journal of Medical Genetics*, vol. 48, no. 9, pp. 580–589, 2011.
- [112] A. B. Singleton, “Exome sequencing: a transformative technology,” *The Lancet Neurology*, vol. 10, no. 10, pp. 942–946, 2011.
- [113] T. Klassen, C. Davis, A. Goldman et al., “Exome sequencing of ion channel genes reveals complex profiles confounding personal risk assessment in epilepsy,” *Cell*, vol. 145, no. 7, pp. 1036–1048, 2011.
- [114] C. S. Ku, E. Y. Loy, Y. Pawitan, and K. S. Chia, “The pursuit of genome-wide association studies: where are we now,” *Journal of Human Genetics*, vol. 55, no. 4, pp. 195–206, 2010.
- [115] H. C. Mefford, H. Muhle, P. Ostertag et al., “Genome-wide copy number variation in epilepsy: novel susceptibility loci

- in idiopathic generalized and focal epilepsies,” *PLoS genetics*, vol. 6, no. 5, article e1000962, 2010.
- [116] V. K. Rakyan, T. A. Down, D. J. Balding, and S. Beck, “Epigenome-wide association studies for common human diseases,” *Nature Reviews Genetics*, vol. 12, no. 8, pp. 529–541, 2011.
- [117] K. Kobow, I. Jeske, M. Hildebrandt et al., “Increased reelin promoter methylation is associated with granule cell dispersion in human temporal lobe epilepsy,” *Journal of Neuropathology and Experimental Neurology*, vol. 68, no. 4, pp. 356–364, 2009.



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