

# Genetic and epigenetic mechanisms of epilepsy: a review

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**Abstract:** Epilepsy is a common episodic neurological disorder or condition characterized by recurrent epileptic seizures, and genetics seems to play a key role in its etiology. Early linkage studies have localized multiple loci that may harbor susceptibility genes to epilepsy, and mutational analyses have detected a number of mutations involved in both ion channel and nonion channel genes in patients with idiopathic epilepsy. Genome-wide studies of epilepsy have found copy number variants at 2q24.2-q24.3, 7q11.22, 15q11.2-q13.3, and 16p13.11-p13.2, some of which disrupt multiple genes, such as *NRXN1*, *AUTS2*, *NLG1*, *CNTNAP2*, *GRIN2A*, *PRRT2*, *NIPA2*, and *BMP5*, implicated for neurodevelopmental disorders, including intellectual disability and autism. Unfortunately, only a few common genetic variants have been associated with epilepsy. Recent exome-sequencing studies have found some genetic mutations, most of which are located in nonion channel genes such as the *LGII*, *PRRT2*, *EFHCI*, *PRICKLE*, *RBFOX1*, and *DEPDC5* and in probands with rare forms of familial epilepsy, and some of these genes are involved with the neurodevelopment. Since epigenetics plays a role in neuronal function from embryogenesis and early brain development to tissue-specific gene expression, epigenetic regulation may contribute to the genetic mechanism of neurodevelopment through which a gene and the environment interacting with each other affect the development of epilepsy. This review focused on the analytic tools used to identify epilepsy and then provided a summary of recent linkage and association findings, indicating the existence of novel genes on several chromosomes for further understanding of the biology of epilepsy.

**Keywords:** epilepsy, genetics, neurodevelopment disorder, neurological disorder

## Introduction

Epilepsy is a common chronic neurological disorders characterized by recurrent seizures due to excessive electrical discharges in a group of brain cells. Seizures are characterized by brief episodes of involuntary shaking that may involve a part or the entire body and sometimes are accompanied by loss of consciousness and loss of bowel or bladder control. While the classification of epilepsy is often evolving clinically, epilepsies tend to have two broad categories: focal and nonfocal epilepsy.<sup>1</sup> Focal epilepsy is defined as a seizure originating within one cerebral hemisphere, whereas the nonfocal epilepsy is mostly a generalized epilepsy (GE). Nonfocal epilepsy such as absence seizure is characterized by a transitory alteration of consciousness, with or without other clinical signs, and each episode lasts between 3 and 30 seconds. Bimodal distribution for age of onset with the first peak at 6–7 years (childhood) and the second peak at ~12 years of age (juvenile) is a feature of typical absence seizure, but it is possible to have an absence seizure at any age. Absence seizures are broadly divided into typical and atypical types: typical absence seizure has a frequency >2.5 Hz and is characterized by transient impairment of consciousness accompanied by one or

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more other features such as staring, behavioral arrest, and eyelid fluttering. Atypical absence seizures have a frequency <2.5 Hz, have less abrupt onset and offset and variable alteration of consciousness, and tend to last longer than typical absence seizures.<sup>1–3</sup> In addition, a smaller proportion of epilepsies are unclassifiable;<sup>2</sup> ~60% of individuals with epilepsy are classified as focal.<sup>3</sup>

The development of epilepsy has a great variation in age and geographic distribution. Epilepsy affects ~1% of worldwide populations at the age of 20 years and 3% at the age of 75 years.<sup>4</sup> According to the World Health Organization (WHO),<sup>5</sup> ~80% of epilepsy cases occur in the developing countries and three-fourth of affected individuals do not get appropriate treatment. The onset of new cases occurs most frequently in infants and the elderly in the developed countries, whereas new cases are often seen in older children and young adults in the less developed world.<sup>6</sup> Therefore, epilepsy may cause a different disease burden between the more developed and the less developed world and has different implications for the etiology.

Epilepsy is believed to have a genetic component. Berkovic et al<sup>7</sup> revealed that environmental insults such as trauma, hypoxia, and vascular lesions may alter function of ion channels and result in altered transcription, thus causing acquired channelopathies. Both the inherited and acquired domains are important for epilepsy genetics. Twin studies suggest that the heritability of epilepsy is ~25%–70% and appears to increase with age. Studies have shown that the probandwise concordance rate is 0.37 in monozygotic twins, which is significantly higher than that in dizygotic twins.<sup>8</sup> A recent study reported that the heritability is 32% for all epilepsy, 23% for focal epilepsy, and 36% for nonfocal epilepsy.<sup>9</sup> While genetic linkage analyses have identified several loci that may harbor susceptibility loci to epilepsy. Recent advances in genomic technology have made it feasible to identify common genetic variants and to screen for copy number variants (CNVs) associated with epilepsies through genome-wide analysis or detect single-point mutations through exome sequencing or whole-genome sequencing. Epilepsy may result from infection and trauma or can also develop because of brain damage from other disorders such as brain tumor, alcoholism, Alzheimer's disease, and stroke.<sup>10</sup>

Recent genetic research has led to the identification of a significant number of genes implicated in monogenic forms of epilepsy. However, other causative genes involved in a considerable proportion of familial epilepsies need to be identified to fully elucidate the etiology of epilepsy. Here, we

provided a review on the genetics of epilepsy by discussing the genetic variants identified through a variety of approaches and epigenetic processes for further understanding of the biology of epilepsy.

## Search strategy

The relevant studies were searched using key words in four acknowledged databases: Web of Science, Springer, Scopus, and MEDLINE. This review screened for studies conducted in the period from 1988 to April 2017 using the following key words: epilepsy, genetics, neurodevelopment disorder, and neurological disorder. A study was included if it matched the corresponding period from 1988 to April 2017. This review included randomized controlled trials (RCTs), observational studies, descriptive studies, web pages, study protocols, seminar papers, retrospective studies, reviews, books, book chapters, and abstracts on the research topic.

## Genetic linkage loci

Genome-wide linkage scans and linkage analyses of some candidate regions have reported about 20 chromosome loci for epilepsy (Table 1). An acquired structural problem in the temporal lobe is a frequent feature of temporal lobe epilepsy (TLE). TLE consists of a heterogeneous group of seizure disorders, such as lateral familial TLE, mesial familial TLE, and familial partial epilepsy with variable foci.<sup>11,12</sup> A single nucleotide polymorphism (SNP)-based linkage study of familial mesial TLE provided a suggestive linkage to chromosome 3q26.<sup>12</sup> Belhedi et al<sup>13</sup> demonstrated that chromosome 22q13.31 has been linked to recessive genetic generalized epilepsy with febrile seizures plus (GEFS+) in a Tunisian consanguineous family.

## Chromosome 2q24

GEFS+ has been linked with mutations of three sodium channel genes and two gamma-aminobutyric acid (GABA)<sub>A</sub> receptor genes. The components of GEFS+ include febrile seizures persisting beyond childhood; afebrile, generalized, tonic-clonic, absence, myoclonic, atonic, uncomplicated febrile seizures; and temporal lobe seizures.<sup>14</sup> The linkage locus 2q24 is localized with both GEFS+ and familial febrile seizures.<sup>15</sup> In families with GEFS+, mutations in gene encoding ligand-gated GABA<sub>A</sub> receptor (GABAR) subunits such as GABRG2 and GABRD cause epilepsy by haploinsufficiency.<sup>14,15</sup> Two distinct regions at 2q24.2–q24.3, harboring possible *SCN* cluster genes and *SLC4A10*, respectively, are linked to idiopathic epilepsy.<sup>16</sup> Interestingly, four of nine genes encoding

**Table 1** Major linkage loci reported for epilepsies

Location	Epilepsy syndrome	Gene	Reference	PMID
2q24	Benign familial infantile convulsions	<i>SCN3A</i>	184	11326335
2q24	GEFS+	<i>SCN1A</i>	15	10521305
2q24	GEFS+	<i>SCN2A</i>	17	18242854
2q24	GEFS+	<i>SCN9A</i>	17	18242854
2q34	GGE		185	22242659
3q26	A benign form of mesial TLE		12	24315020
5q34	A broad spectrum of familial GGE syndromes		185	22242659
5q14-q15	Febrile seizures and epilepsy		186	16273391
6p12	JME		187	12439895
6p21.3	JME	<i>TAP-1</i>	188	12830434
6p21.3	JME	<i>BRD2</i>	20	1901453
6q24	Lafora progressive myoclonus epilepsy	<i>EPM2A</i>	24	9345091
7p12.1-7q11.22	PME	<i>KCTD7</i>	27	25060828
7q32	Myoclonic seizures-related photosensitivity		189	17123300
8q24	IGE	<i>KCNQ3</i>	192	8528209
8q24	CAE	<i>KCNK9</i>	32	9758624
10q24	Partial epilepsy		130	7647791
	ADPEAF		39	11879388
10q22-24	ADPEAF	<i>LGII</i>	128	11978770
10q25-q26	Generalized tonic-clonic seizure		190	16130088
13q31.3	GGE		185	22242659
15q14	RE		191	9855510
16p13	Familial autodominate recessive IME of infancy	<i>TBC1D24</i>	40	10741954
19q13	GEFS+	<i>SCN1B</i>	185	22242659
22q11-12	Familial partial epilepsy with variable foci	<i>DEPDC5</i>	193	20659149
22q13.11	Recessive genetic epilepsy with febrile seizures plus	<i>TBC1D22A</i>	13	24067191

**Abbreviations:** GEFS+, generalized epilepsy with febrile seizures plus; GGE, genetic generalized epilepsy; TLE, temporal lobe epilepsy; JME, juvenile myoclonic epilepsy; PME, progressive myoclonic epilepsy; IGE, idiopathic generalized epilepsy; CAE, childhood absence epilepsy; ADPEAF, autosomal dominant partial epilepsy with auditory features; RE, rolandic epilepsy; IME, infantile myoclonic epilepsy.

the sodium channel pore-forming  $\alpha$  subunits, *SCN1A*, *SCN2A*, *SCN3A*, and *SCN9A*, are located on the 2q24.3 locus.<sup>17</sup> *MASS1* was mapped to chromosome 5q14 and a loss-of-function mutation in *MASS1* was associated with seizure phenotype, but *MASS1* gene was not likely to be a contributing factor in most families with febrile seizures.<sup>14-17</sup>

### Chromosome 6p21.3

Juvenile myoclonic epilepsy (JME) is one of the most common forms of idiopathic generalized epilepsy (IGE), and a locus for JME linked to human leukocyte antigen on chromosome 6p21.3 was originally termed EJM1 (OMIM 254770).<sup>18-20</sup> Pal et al<sup>21</sup> revealed that microsatellite marker for the bromodomain-containing 2 (*BRD2*) locus on chromosome 6p21.3 was associated with a highly significant linkage disequilibrium with several SNPs. They also found that along with two SNPs in the promoter region of *BRD2*, one haplotype (rs620202-rs516535-brd2-rs635688-rs2066741, G-C-6-T-T) was also associated with JME. *BRD2* (RING3) is a putative nuclear transcriptional regulator from a family of

genes that is expressed during development, suggesting that abnormalities in neural development may be a cause of common idiopathic epilepsy. Another candidate gene identified in the 6p21.3 locus is the transporter 1 ATP-binding cassette sub-family B (*TAP-1*), a gene encoding the transporter associated with antigen processing that may be a susceptibility factor to JME.<sup>22</sup> *CLCN2* encodes the voltage-gated chloride channel *ClC-2*, and it is regarded as a predisposing gene for IGE. *CLCN2* mutation impairs GABAergic neurotransmission in the brain by altering chloride gradient across the cellular membrane.<sup>18-20</sup> *CACNB4* encodes a member of the beta subunit family of voltage-dependent calcium channel complex protein, and mutations in this gene have been associated with IGE juvenile episodic ataxia, type 5, and myoclonic epilepsy.<sup>18,19</sup> *JRK/JH8*, which maps to 8q24, has been associated with some forms of IGE.<sup>18</sup>

The genetic mechanisms of *BRD2* associated with epilepsy might be because 1) *BRD2* haploinsufficiency is associated with a deficit in GABAergic neurons, which lead to an increased susceptibility to provoked seizure and

2) haploinsufficiency is associated with the basal ganglia path in structures, critical for control of seizure activity.<sup>23</sup>

## Chromosome 6q24

Sainz et al<sup>24</sup> reported an extended area of homozygosity on chromosome 6q23-25 in nine patients of Lafora progressive myoclonus epilepsy from four families with consanguineous marriages. Using positional cloning, a novel gene epilepsy progressive myoclonus type 2A (*EPM2A*) gene was identified.<sup>25</sup> So far distinct mutations in *EPM2A* and *EPM2B* (or *MALIN*) have been discovered in patients with the Lafora progressive myoclonus epilepsy in over 200 independent families with the Lafora disease. Among these mutations, half of them are missense mutations and one-quarter are deletions.<sup>26</sup> *EPM2A* encodes a protein with consensus amino acid sequence, indicative of a protein tyrosine phosphatase (PTP), whereas *EPM2B* encodes an ubiquitin ligase. Mutations in these regions show a critical impact on the functionality of laforin, which works together with malin as a complex to promote the degradation of malin targets through the ubiquitin-proteasome system.

## Chromosome 7p12.1-7q11.22

A homozygous region on chromosome 7p12.1-7q11.22 has been identified for progressive myoclonic epilepsy (PME). Multiple mutations (eg, p.Tyr276Cys and p.R94W) are detected for PME in potassium channel tetramerization domain-containing 7 (*KCTD7*).<sup>27-29</sup> *KCTD7* is a member of the *KCTD* gene family. It is predominantly expressed in the brain to hyperpolarize cell membrane and reduce the excitability of transfected neurons.<sup>27</sup> The effect on the plasma membrane resting potential is possibly mediated by *KCTD7* in interaction with Cullin-3, an ubiquitin-ligase component.<sup>30</sup>

## Chromosome 8q24

Chromosome 8q24 has been found to be associated with IGE, familial adult myoclonic epilepsy,<sup>31</sup> and childhood absence epilepsy (CAE).<sup>32</sup> A mutation in Twik-like acid-sensitive K<sup>+</sup> channel (*KCNK9*) was revealed in a genetic model of absence epilepsy.<sup>33</sup> *KCNK9* encodes K<sub>2p</sub>9.1, a protein that contains multiple transmembrane regions and two pore-forming P domains and functions as a pH-dependent potassium channel. A standard karyotype analysis had detected a 2.3 Mb duplication of chromosome 8q24.3 associated with severe mental retardation and epilepsy.<sup>34</sup> Unfortunately, previous mutational screening of 8q24.3 in epilepsy failed to find any association with variants in *JRK/JH8* or *ARC*, genes that have

been implicated in other neuropsychiatric disorders such as schizophrenia and bipolar.<sup>35,36</sup>

## Chromosome 10q24

An initial linkage evidence was detected in a 10 cM interval on 10q in a large pedigree with 10 individuals affected with partial epilepsy,<sup>37</sup> which was replicated in a follow-up study of a four-generation family with nine individuals affected with temporal partial epilepsy.<sup>38</sup> Another follow-up linkage study in the four multiplex families with autosomal dominant partial epilepsy with auditory features (ADPEAF) also confirmed this linkage locus.<sup>39</sup> Mutation in the *LGII* gene/*Epitempin* on 10q24 may cause autosomal dominant lateral temporal epilepsy (ADLTE).

## Chromosome 16p13.3

A genome-wide linkage scan in a large Italian pedigree segregating recessive idiopathic myoclonic epilepsy mapped a linkage locus on chromosome 16p13. Haplotype analysis defined the critical region within a 3.4-cM interval between D16S3024 and D16S423.<sup>40</sup> Mutations including two compound heterozygous missense mutations (D147H and A509V) in *TBC1D24* were identified for familial infantile myoclonic epilepsy.<sup>41-44</sup> The gene mutations together with its predominant expression in critical epileptogenic brain areas highlighted that *TBC1D24* plays a fundamental role in the regulation of neuronal network excitability. In situ hybridization analysis revealed that *TBC1D24* is mainly expressed in the cerebral cortex and the hippocampus. *TBC1D24* modulates the small GTPase ADP-ribosylation factor 6 (ARF6), which has been implicated for the modulation of brain excitability and regulates neuronal migration and maturation through modulation of the ARF6-dependent pathway.<sup>44</sup>

## CNVs

CNVs are alterations in the DNA that results in the cell having an abnormal variation in the number of copies of one or more sections of the DNA. CNVs are caused by structural rearrangements of the genome, such as deletions, duplications, inversions, and translocations; they are causes of some nervous system disorders.<sup>45</sup> Methods for the direct detection of CNVs across the whole genome have become effective instruments for identifying genetic risk factors of human diseases.<sup>46</sup> CNVs can be private and recurrent, normally rare but highly penetrant for a disease. While the private CNVs can occur anywhere across the genome, the recurrent CNVs occur at genomic hot spots that can increase

**Table 2** Summary of CNVs identified for epilepsy

Locus	CNVs	Genes	Reference	Accession ID
2p16.3	Exon-disrupting deletions	<i>NRXN1</i>	12	25243798
2q24.2-q24.3	Duplication/deletion	<i>SCN1A, SCN2A</i>	194	23016767
6p12.1	Microduplication	<i>BMP5</i>	57	25923336
7q11.22	Deletion	<i>AUTS2</i>	48	20502679
7q32.3	Microdeletion	<i>PODXL</i>	57	25923336
7q35	Deletion, hemizygous deletions	<i>CNTNAP2</i>	48	20502679
15q11.2	Microdeletion	<i>NIPA2, CYFIP1</i>	49	19843651
15q13.3	Microdeletion	<i>CHRNA7</i>	48	20502679
16p13.11	Deletion	<i>NDE1</i>	51	22523559
16p13.2	Microdeletion	<i>GRIN2A, PRRT2</i>	61	24372385

**Abbreviation:** CNV, copy number variant.

the risk of a range of disorders. One CNV often disrupts multiple genes and therefore may cause multiple diseases or a syndrome.

CNVs vary according to phenotype and have been reported in up to 28% of patients with epilepsy.<sup>47</sup> Genome-wide analysis of 517 individuals with epilepsy and 2,493 controls suggests that 8.9% of patients carry one and more rare CNVs that were not present in controls. Of these CNVs, 2.9% of patients have deletions at loci 15q11.2, 15q13.3, or 16q13.11, which are genomic hotspots previously associated with intellectual disability, autism, and schizophrenia.<sup>48</sup> Similar deletions were confirmed in several independent samples.<sup>49–52</sup> Other studies<sup>53–56</sup> have also found recurrent distal deletion at 7q11.22, maternally derived duplication at 15q11.2-q13.3, duplication of 16p11.2, and duplication of 16p13 in patients with epilepsy (Table 2). In patients with infantile epilepsy, duplication at 2q24.2-q24.3 was found. In a recent study, microduplication at 6p12.1 and microdeletion at 7q32.3, predicting *BMP5* and *PODXL*, respectively, were found in multiple patients with epilepsy or epilepsy plus mental retardation or with JME.<sup>57</sup>

In patients with IGEs, recurrent microdeletions were found more frequent at 15q11.2.<sup>49</sup> The 15q11.2 microdeletion disrupted non-imprinted genes in Prader–Willi syndrome (PWS)/Angelman syndrome (AS) 2 (*NIPA2*) in patients with CAE<sup>58</sup> and schizophrenia<sup>59</sup> in two independent studies in the Han Chinese populations. This region contained four highly conserved and non-imprinted genes, *NIPAI*, *NIPA2*, *CYFIP1*, and *TUBGCP5*. A study of 52 patients carrying this CNV found that 15q11.2 was prevalent in neurodevelopment disorders such as developmental delay (68.3%), speech impairment (85.4%), and psychological issues (63.4%) that included attention-deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD), or obsessive-compulsive disorder (OCD), and 18.7% of patients were

noted with seizures and 17.3% with associated congenital heart diseases.<sup>60</sup>

Several other deletions that disrupt multiple genes are also detected for neurodevelopmental disorders, such as autism, schizophrenia, mental retardation, and epilepsy. In the 16p13.11 deletion, the gene nuclear distribution protein nudE homolog 1 (*NDE1*) is suspected as the leading disease-causing gene at 16p13.11.<sup>51</sup> A novel 16p13.2 microdeletion, disrupting ionotropic glutamate *N*-methyl-D-aspartate (NMDA) receptor subunit 2A (*GRIN2A*) and *proline-rich transmembrane protein 2* (*PRRT2*), is detected in patients with rolandic epilepsy (RE).<sup>61</sup> A 20-kb microdeletion was found in two sisters with auditory focal seizure at 200 kb away from exon 1 of *NRXN1*, and in the same family, a 50.5-kb microdeletion within the neuroligin 1 (*NLGN1*) gene at 3q26.31 was co-segregated with both lateral temporal epilepsy and with the *NRXN1* deletion simultaneously.<sup>62</sup> Deletions in *AUTS2* and *CNTNAP2* implicated for other neurodevelopmental disorders such as autism may also cause epilepsy.<sup>48,63</sup> Kim et al<sup>64</sup> revealed that patients with 22q11.2DS tend to have a higher risk of epilepsy.

Chromosome translocations may cause epilepsy. A de novo balanced translocation t(6;22)(p21.32;q11.21) has been detected in patients with epilepsy with myoclonic absences (EMA) and intellectual disability.<sup>65</sup> The breakpoint, between exon 5 and exon 6 of *SYNGAP1*, is found to truncate the NMDA receptor-associated gene *SYNGAP1*, encoding the synaptic Ras GTPase activating protein 1. The protein is a major component of the postsynaptic density, exclusively expressed in the brain, predominantly in the cortex, hippocampus, and olfactory bulb, and it is activated using NMDA receptor activator.<sup>66</sup> Mutations in *SYNGAP1* may result in nonsyndromic intellectual disability.<sup>65</sup> Dysfunction of *SYNGAP1* contributes to the development of generalized EMA. Another translocation involving chromosome

6p21, t(4;6) (q35;p21), is reported in two patients with IGE within a nuclear family.<sup>67</sup> A de novo duplication, found in a single patient with epilepsy and development delay, is likely linked to genes (*GABBR1*, *BRD2*, and *GRM4*) that are involved with brain function and synaptic transmission.<sup>68</sup>

## Common genetic variants

Genome-wide association studies have successfully identified numerous susceptibility genes for epilepsy. Using two cohorts of case-control samples from Hong Kong and Taiwan, a study showed that two SNPs rs2292096 and rs6660197 located at *CAMSAP1L1* on 1q32.1 were associated with epilepsy at a genome-wide significance.<sup>69</sup> Aside from rs702416 in *KCND2*, the rs1980416 at *DSCAM* and rs13020314 at *ERBB4* were also associated with epilepsy. *ERBB4* encodes ErbB4, a member of the type I receptor tyrosine kinase subfamily that promotes synapse formation of GABA-containing interneurons in the hippocampus. Two SNPs rs9390745 and rs4840200 at *GRIK2* (encoding GluR6, glutamate ionotropic receptor, kainate 2) on 6q21 also showed strong association signals in the discovery sample. Meta-analysis<sup>70</sup> of 12 genome-wide association studies, including nine cohorts of European ancestry populations, two African-Americans, and one Chinese from Hong Kong and Taiwan, suggested that common variants at *SCN1A* and *PCDH7* are associated with epilepsies. Several other variants at *GOLIM4*, *GABRA2*, *VRK2/FANCL*, and *MMP8* are likely associated with different forms of epilepsy, although not genome-wide significant.

Candidate gene approach elucidated several common variants or mutational variants associated with epilepsy. Consistent genetic associations with epilepsy have been observed in carboxypeptidase A6 (*CPA6*) on 8q13.2 and the calcium homeostasis modulator 1 (*CALHM1*) on 10q24.33.<sup>71–73</sup> *CPA6* protein plays a role in the activation of peptides that have neuroprotective effects or in the inactivation of peptides that cause neuronal stimulation. Mutations of G267R and A270V in *CPA6* are linked to familial TLE. These mutations cause a decreased level of *CPA6* protein in the extracellular matrix. The reduction in *CPA6* activity may lead to epilepsy by an imbalance of excitation and inhibition.<sup>72,74</sup> *CALHM1* encodes calcium channel, interferes with calcium homeostasis and increases amyloid beta (A $\beta$ ) levels. *CALHM1* rs2986017 might be associated with an increased risk for Alzheimer's disease in multiple populations.<sup>75–77</sup> However, there are multiple inconsistent replications.<sup>78</sup> In an analysis of five SNPs in *CALHM1*, an SNP rs11191692 was associated with TLE after correction for multiple testing, and a haplotype analysis of five SNPs provided a support that this association

was independent of apolipoprotein E (APOE) epsilon 4.<sup>79</sup> *APOE*, a gene widely associated with neurological disorders and some cardiovascular traits, was also associated with TLE. A meta-analysis of seven published studies showed that carrying of *APOE4* allele tends to have an early age at the onset of TLE.<sup>80</sup>

## Rare mutational variants

Exome sequencing is a technique for sequencing all the protein-coding genes in the genome. It is an effective approach to study rare Mendelian diseases. Exome-sequencing analysis has opened an avenue to discover genetic variants for epileptogenesis across the whole genome and to determine the physiologic effects of mutations in epilepsy-associated genes.<sup>81</sup> Because of genetic heterogeneity or population stratification, however, exome sequencing is likely difficult in detecting rare variants associated with complex disorders in a population-based sample such as unrelated cases and controls. For example, through exome sequencing of 237 channel genes in cases and controls, Klassen et al<sup>82</sup> found little evidence or biological rationale for an SNP load effect in ion channelopathy. Another study using exome sequencing followed by genotyping in a larger sample failed to identify single rare variants of large effect in IGE.<sup>83</sup> Whole-genome sequencing has revealed a de novo *SCN8A* mutation and de novo mutations in *HCN1*.<sup>81–83</sup> Other examples of recent gene discoveries are listed in Table 3. Exome-sequencing analysis of family samples has detected >200 rare variants in ~20 genes in patients with epilepsies, of which some have been recommended by the International League Against Epilepsy (ILAE) as likely causal variants for idiopathic epilepsy (Table 4). While most of these variants are identified in individual families with a small sample size, only a small portion (<3%) of these variants is found in the 1000 Genomes Project database or NHLBI Exome Variant Server (EVS). This suggests that using exome-sequencing approach to identify rare variants in the family with individuals affected with epilepsy is robust.<sup>84</sup> These rare variants are mostly located in genes encoding for ion channels, including voltage-gated sodium, potassium, calcium, chloride channels, and receptors such as ligand-gated GABAA, glutamate, and acetylcholine receptors.

## Ion channel gene mutations

Ion channel is a protein macromolecule spanning a biological membrane that allows ions to pass from one side of the membrane to the other.<sup>85</sup> There are two types of ion channel: voltage gated and leakage. A voltage-gated ion channel can be opened or closed at some circumstances. The opening of

**Table 3** Whole-exome sequencing found variants associated with epilepsy

Locus	Gene symbol	Product	Phenotype
2q35	INHHA	Inhibin, alpha	EGTCA
3p14.1	PRICKLE2	Homolog 2 on chromosome 3	PME
4q21.1	SCARB2	Scavenger receptor class B, member 2	PME
6p21.3	SYNGAP1	Synaptic RasGTPase activating protein 1	EMA
12q12	PRICKLE	Prickle homolog 1 on chromosome 12	PME
13q34	CARS2	Csteinyln-tRNA synthetase 2, mitochondrial (putative)	PME
15q23	CLN6	Ceroid-lipofuscinosis, neuronal 6	TOPME
17q21.34	GOSR2	Golgi SNAP receptor complex member 2	PME
16p11.2	PRRT2	Proline-rich transmembrane protein 2	BFNIS
16p13.3	RBFOX1	RNA-binding protein, fox-1 homolog ( <i>C. elegans</i> ) 1	IGE/RE
17q25.3	RBFOX3	RNA-binding protein, fox-1 homolog ( <i>C. elegans</i> ) 3	RE
21q22.3	COL6A2	Collagen type VI alpha 2	PME
22q12	DEPDC5	Dishevelled, Egl-10 and Pleckstrin domain-containing protein 5	ADFE

**Abbreviations:** EGTCA, epilepsy with generalized tonic-clonic seizures on awakening; PME, progressive myoclonus epilepsy; EMA, epilepsy with myoclonic absences; TOPME, teenage-onset progressive myoclonus epilepsy; *C. elegans*, *Caenorhabditis elegans*; IGE, idiopathic generalized epilepsy; RE, rolandic epilepsy; ADFE, autosomal dominant focal epilepsy.

voltage-gated ion channel can be archived by either a voltage change across the membrane or a binding of a chemical substance such as a ligand to a receptor in or near the channel (chemically activated or ligand-gated channel).

### Voltage-gated sodium channels

Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials in neurons

and other electrically excitable cell.<sup>86</sup> They include nine  $\alpha$  subunits named  $Na_v 1.1$ – $Na_v 1.9$  that are encoded by the gene from *SCN1A*–*SCN11A*, respectively, in which the *SCN6/7A* gene is part of the  $Na_x$  subfamily, and four  $\beta$  subunits named  $Na_v \beta 1$ – $Na_v \beta 4$  that are encoded by *SCN1B*–*SCN4B*, respectively. In the mammalian brain, normally voltage-gated sodium channels consist of an  $\alpha$  subunit that forms the ion conduction pore and one to two  $\beta$  subunits, but only

**Table 4** Genetic loci identified and recommended for genetic testing in epilepsy by ILAE

Locus	Gene	Product	Phenotype	ILAE
1q21-23	ATP1A2	Sodium-potassium ATPase	RE	*
19p13	CACNA1A	Cav2.1 (calcium channel)	AE	*
8p21	CHRNA2	$\alpha 2$ subunit (nACh receptor)	ADNFLE	*
20q13.2-q13.3	CHRNA4	$\alpha 4$ subunit (nACh receptor)	ADNFLE	*
1q21	CHRNA2	$\beta 2$ subunit (nACh receptor)	ADNFLE	*
6p12-p11	EFHC1	EF-hand motif protein	JME	*
5q34-q35	GABRA1	$\alpha 1$ subunit (GABAR)	JME	*
5q34	GABRG2	$\gamma 2$ subunit (GABAR)	GEFS+	*
15q12	GABRB3	GABAR, beta 3	CEA	
16p13.2	GRIN2A	Glutamate receptor, ionotropic, NMDA 2A	RE	
12p13	KCNA1	Kv1.1 (potassium channel)	FE	*
10q22	KCNMA1	Calcium-activated potassium channels	GE	*
3q26.3-q27	KCNMB3	Potassium large conductance calcium-activated channel, subfamily M beta 3	JAE	
1q23.2	KCNJ10	Potassium inwardly rectifying channel, subfamily J, member 10	IGE	
20q13.3	KCNQ2	Kv7.2 (potassium channel)	BFNS	*
8q24	KCNQ3	Kv7.3 (potassium channel)	BFNS	*
9q34.3	KCNT1	Potassium channel, subfamily T, member 1	ADNFLE	
10q24	LGI1	LRR protein	ADLTE	*
19q13.1	SCN1B	$\beta 1$ subunit (sodium channel)	GEFS+	*
2q23-q24.3	SCN2A	Nav1.2 (sodium channel)	BFNIS	*
1p35-p31.1	SLC2A1	GLUT1	IGE	*
9q34.1	STXBPI	Syntaxin-binding protein 1	EIEE	*

**Note:** \*Recommended for genetic testing in epilepsy by ILAE.

**Abbreviations:** ILAE, International League Against Epilepsy; RE, rolandic epilepsy; AE, absence epilepsy; ADNFLE, autosomal dominant nocturnal frontal lobe epilepsy; JME, juvenile myoclonic epilepsy; GABAR, GABA<sub>A</sub> receptor; GEFS+, genetic epilepsy with febrile seizures plus; CEA, childhood absence epilepsy; NMDA, N-methyl-D-aspartate; FE, focal epilepsy; GE, generalized epilepsy; JAE, juvenile absence epilepsy; IGE, idiopathic generalized epilepsy; BFNS, benign familial neonatal idiopathic generalized epilepsy; LRR, leucine-rich repeat; ADLTE, autosomal dominant lateral temporal epilepsy; GLUT1, glucose transporter type 1; EIEE, early infantile epileptic encephalopathy with suppression-burst.

the  $\alpha$  subunit is required for function.<sup>87</sup> Genetic epilepsy syndromes with a wide range of severity may result from voltage-gated sodium channel mutation. Benign neonatal infantile seizure is caused by mutations in  $\text{Na}_v1.2$  channels, and patients may experience episodes of discoordination and continuous muscle movement (myokymia) between attacks of ataxia.<sup>86,87</sup>

Mutations in the genes encoding for  $\alpha$  subunits play an important role in the development of epilepsy. Following up the linkage locus 2q24, sequencing of *SCN1A* demonstrated that individuals affected with epilepsy are heterozygous for missense mutations (T875M and R1648H).<sup>88</sup> Direct sequencing of *SCN1A* revealed a novel heterozygous mutation (c.5383G>A) in one Chinese family with GEFS+.<sup>89</sup> Two novel mutations (p.V1612I and p.C1756G) in *SCN1A* were identified in Indonesian patients with severe myoclonic epilepsy in infancy.<sup>90</sup>

So far, >800 mutations in genes encoding neuronal  $\text{Na}_v$  channels, including *SCN1A* and *SCN2A*, have been described in patients with epilepsy.<sup>91</sup> Many of these mutations are sporadic and cause loss of function, which demonstrates haploinsufficiency of *SCN1A*.<sup>92</sup> In *SCN2A*, a heterozygous de novo nonsense mutation R102X is found with intractable epilepsy plus mental decline.<sup>93</sup> The de novo missense mutation (p.Ala263Val) in *SCN2A*, which leads to a pronounced gain of function, is found with neonatal-onset seizures and variable episodes of ataxia.<sup>94</sup> Only a few mutations,<sup>17</sup> such as a charge-neutralizing mutation K345Q and four novel missense variants (R357Q, D766N, E1111K, and M1323V), are found in *SCN3A* with focal epilepsy in children.<sup>91</sup>

In addition, a mutation in *SCN1B* predicting a deletion of five amino acids was found in a family with both febrile seizure and early onset absence epilepsy.<sup>95</sup> The genes *SCN1A*, *SCN1B*, and *SCN2A* have been recommended by the ILAE for genetic testing in epilepsy.

### Voltage-gated potassium channels

Potassium channels are a diverse family of membrane proteins that are present in both excitable and non-excitable cells found in all living organisms. Members of this channel family play critical roles in cellular signaling processes regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, smooth muscle contraction, and cell volume.<sup>96</sup> Based on the primary amino acid sequence of the pore-containing subunit, potassium channels are generally classified into: 1) six transmembranes with one-pore channel (voltage-gated potassium channels); 2) two transmembranes with one-pore channel (inward rectifier

$\text{K}^+$  channels); 3) the calcium-activated potassium channels; and 4) four transmembranes with two-pore channels.

The voltage-gated potassium channels ( $\text{K}_v$ ) include  $\alpha$  and  $\beta$  subunits. While  $\alpha$  subunits form the actual conductance pore,  $\beta$  subunits are auxiliary proteins that associate with  $\alpha$  subunits. There are about 40 known human voltage-gated potassium channel  $\alpha$  subunits that can be grouped into 12 classes, labeled as  $\text{K}_v\alpha1-12$  or  $\text{K}_v1-12$ .<sup>97</sup> The grouping is according to function and then subgrouped according to the  $\text{K}_v$  sequence homology classification scheme. The most common class includes the Shaker-related potassium channels  $\text{K}_v1.1-1.7$ , which is encoded by *KCNA1-KCNA7*. Human ether-a-go-go-related  $\text{K}^+$  channels  $\text{K}_v11.1$  or hERG,  $\text{K}_v11.2$ , and  $\text{K}_v11.3$  are encoded by *KCNH2*, *KCNH6* and *KCNH7*, and *KCNQ* channels, respectively.  $\text{K}_v7.1-7.5$  is encoded by *KCNQ1-KCNQ5*.<sup>98</sup> In addition, the known human calcium-activated ( $\text{K}_{ca}$ ) channels are grouped into  $\text{K}_{ca}2/3$  ( $\text{K}_{ca}2.1$ ,  $\text{K}_{ca}2.3$ ,  $\text{K}_{ca}2.3$ , and  $\text{K}_{ca}3.1$ , encoded by *KCNN1-KCNN4*, respectively) and  $\text{K}_{ca}1/4/5$  ( $\text{K}_{ca}1.1$ ,  $\text{K}_{ca}4.1$ ,  $\text{K}_{ca}4.2$ , and  $\text{K}_{ca}5.1$ , encoded by *KCNMA1*, *KCNT1*, *KCNT2*, and *KCNUI*, respectively).<sup>99</sup> The inward rectifier  $\text{K}^+$  channels consist of seven subfamilies denoted as  $\text{K}_{ir}1-7$ .

Mutations in multiple genes in the voltage-gated potassium channels are detected in epilepsy. They include mutations in *KCNA1* in families with autosomal dominant episodic ataxia type 1 (EA1) and epilepsy.<sup>100</sup> *KCNA1* mutations have been associated with phenotypic variability and may increase vagus nerve activity sufficiently to cause sudden unexplained death in epilepsy.<sup>97-100</sup> A mutation in *KCNMA1* has been identified in a family with generalized epilepsy and paroxysmal dyskinesia (GEPD), and multiple mutations in *KCNQ2* and *KCNQ3* were associated with benign familial neonatal convulsion or epilepsy.<sup>101,102</sup> *KCNMA1* encodes the  $\alpha$  subunit of the large conductance, voltage-gated, and calcium-activated  $\text{K}^+$  channel. The four loci *KCNA1*, *KCNMA1*, *KCNQ2*, and *KCNQ3* are recommended for genetic testing in epilepsy by the ILAE.

Mutations in several other genes such as *KCNH1*, *KCND2*, and *KCTD7* encoding for potassium channels are implicated for epilepsy. Damaging de novo mutations in *KCNH1* ( $\text{K}_v10.1$ ) were found in six individuals with Temple-Baraitser syndrome (TBS), in which two mothers of children with TBS had epilepsy.<sup>103</sup> Whole-exome sequencing of a family with identical twins affected with autism and severe intractable seizures found the de novo mutation p.Val404Met in *KCND2*.<sup>104</sup> A homozygous missense mutation (p.R94W) in a highly conserved segment of exon 2 of *KCTD7* was found in two independent families with PME.<sup>29</sup>



Recently, whole-exome sequencing of a family with three daughters affected with PME and ataxia revealed an additional mutation p.Tyr276Cys in *KCTD7*.<sup>27</sup> The gene *KCNJ10* encoding a member of the inward rectifier-type potassium channel family has been implicated in multiple neurological disorders, including epilepsy. A common missense variation (Arg271Cys) in *KCNJ10* is associated with susceptibility to both focal and generalized epilepsies as well as common IGE syndromes.<sup>105</sup> Heterozygous missense mutations in *KCNJ10* may cause epilepsy, ataxia, sensorineural deafness, and tubulopathy (EAST).<sup>106,107</sup> *KCNJ10* is characterized by having a greater tendency to allow potassium to flow into a cell. It may affect the potassium-buffering action of glial cells in the brain.

Genes in the sodium-activated and calcium-activated potassium channels are implicated for epilepsy. A missense heterozygous de novo mutation p.Phe932Ile in *KCNT1* is identified for severe epilepsy.<sup>108</sup> Several mutations (M896I, R398Q, Y796H, and R928C) have been recently detected in severe cases of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).<sup>109</sup> The gene mutations may increase the sensitivity of potassium channel to cytosolic sodium concentrations, which account for increased excitability. *ADNFLE/NFLE* is characterized by clusters of brief stereotyped seizures and generally occurs during light sleep. Sometimes it is preceded by psychiatric symptoms and occurs mostly during non-rapid eye movement sleep.<sup>109</sup> *KCNT1* gene encodes a sodium-activated potassium channel subunit, which is thought to function in ion conductance and developmental signaling pathways. In addition, a genetic locus for familial febrile seizures and epilepsy has been localized on chromosome 3q26.2-q26.33 and a single base pair deletion (delA750) in exon 4 of *KCNMB3* at this locus was found.<sup>110</sup> *KCNMB3* encodes for calcium-activated potassium channel subunit beta-3 and alters or truncates the terminal 21 amino acids of the three subunits. *KCNMB3* delA750 mutation confers susceptibility to common IGE syndrome.<sup>111</sup>

### Voltage-gated calcium channels

Calcium is a very important signaling molecule that mediates muscle contraction, neurotransmission, and gene transcription.<sup>112</sup> The voltage-gated calcium channels are key transducers of membrane potential changes into intracellular  $\text{Ca}^{2+}$  transients that initiate many physiological events. The channels are multi-subunit proteins comprising a large pore-forming  $\alpha_1$  subunit and four other types of subunits, including  $\alpha_2$ ,  $\delta$ , an intracellular  $\beta$ , and transmembrane glycoprotein  $\gamma$ .

The latter four types are auxiliary subunits and may not be directly involved with conducting calcium or voltage gating.<sup>112</sup> According to amino acid sequence, in mammals, the principal  $\alpha_1$  subunits have ten members grouped into three subfamilies, including  $\text{Ca}_v1$ s,  $\text{Ca}_v2$ s, and  $\text{Ca}_v3$ s. The  $\text{Ca}_v1$ s comprises  $\text{Ca}_v1.1$ ,  $\text{Ca}_v1.2$ ,  $\text{Ca}_v1.3$ , and  $\text{Ca}_v1.4$  that are encoded by *CACNA1S*, *CACNA1C*, *CACNA1D*, and *CACNA1F*, respectively; the  $\text{Ca}_v2$ s includes  $\text{Ca}_v2.1$ ,  $\text{Ca}_v2.2$ , and  $\text{Ca}_v2.3$  that are encoded by *CACNA1A*, *CACNA1B*, and *CACNA1E*, respectively; and the  $\text{Ca}_v3$ s includes  $\text{Ca}_v3.1$ ,  $\text{Ca}_v3.2$ , and  $\text{Ca}_v3.3$  that are encoded by *CACNA1G*, *CACNA1H*, and *CACNA1I*, respectively. While  $\text{Ca}_v1$ s and  $\text{Ca}_v2$ s are high-voltage activated members, the  $\text{Ca}_v3$ s is a low-voltage activated member. A mutation in the  $\text{Ca}_v2.1$  channel has been linked to both generalized and complex partial seizures and severe neurological disorders, including ataxias and congenital migraine.<sup>112,113</sup> Mutations in multiple genes encoding for the calcium channels are implicated for epilepsy. A proband with complex phenotype comprising primary GE is heterozygous for an exon 36 mutation (C5733T) in *CACNA1A*.<sup>113</sup> Mutations in *CACNA1A* have a strong link with familial hemiplegic migraine, episodic ataxia type 2, and spinocerebellar ataxia type 6.<sup>114</sup> Family based studies have also found some common genetic variants in *CACNA1A* associated with IGE.<sup>115,116</sup> In addition, two mutations (R482X and C104F) in *CACNB4* are detected in epilepsy.<sup>117</sup> In screening for mutations in 38 *SCN1A*-mutation-positive probands with myoclonic epilepsy in infancy (SMEI), a missense mutation (R468Q) in *CACNB4* was detected in one proband.<sup>118</sup>

### Nicotinic acetylcholine receptors (nAChRs)

nAChRs are cholinergic receptors that form ligand-gated ion channels in the plasma membranes of certain neurons on the presynaptic and postsynaptic sides of the neuromuscular junction. As ionotropic receptors, nAChRs are directly linked to ion channels. In all, 17 different genes encode for ACh receptor subunits, including ten  $\alpha$ , four  $\beta$ , and  $\gamma$ ,  $\delta$ , and  $\epsilon$  subunits. The  $\alpha$  subunits are principal, and others are complementary.

Several genes encoding for nAChRs are implicated for some rare forms of epilepsy. A missense mutation in *CHRNA4* that replaces serine with phenylalanine at codon 248 was found in all 21 affected family members with ADNFLE, but not in 333 healthy control subjects.<sup>119</sup> Two mutations (V287L and V287M) in *CHRNB2* were also detected in patients with ADNFLE.<sup>120</sup> Mutations in *CHRNA2* were detected in an Italian family with nocturnal frontal lobe

epilepsy (NFLE), but they were not found in 47 families affected with ADNLE.<sup>121</sup> These three genes have been recommended for genetic testing in epilepsy by the ILAE.

### GABARs

The GABARs are one of the two classes of the GABA receptors that respond to the neurotransmitter GABA. GABARs, known as ionotropic receptors, are ligand-gated ion channels that mediate most fast synaptic inhibition in brain. Mutation in GABAR subunit expression and function may result in epileptogenesis. There are 19 genes that encode a number of different GABAR subunits, including  $\alpha_{1-6}$ ,  $\beta_{1-3}$ , and  $\gamma_{1-3}$ , and several other subunits. Mutations in *GABRA1* and *GABRG2* have been recommended by the ILAE for genetic testing in epilepsy. Recently, mutation R46W in the GABAR *GABRA6* was detected in patients with CAE, and it was located in a region homologous to a *GABRG2* missense mutation, R82Q, that was associated with both CAE and febrile seizures in human beings.<sup>122</sup> Mutations (P11S, S15F, and G32R) in the GABAR  $\beta_3$  subunit gene (*GABRB3*) are found in multiple families with CAE.<sup>123</sup> *GABRB3* is located at the human chromosome 15q11-13 complex locus, which contains two GABARs (*GABRA5* and *GABRG3*). PWS and AS are unique clinical disorders that may arise from deletion of chromosome 15q11-q13 during paternal or maternal gametogenesis, respectively.<sup>124</sup> *GABRB3* is regulated by epigenetic modulation and highly expressed in embryonic brain, where repressor-element-1-silencing transcription factor (REST) regulates neuronal genes. Reduced expression of *GABRB3* and *UBE3A*, both of which are within a close genomic region, is observed in each of three neurological syndromes (Rett syndrome, AS, and autism) as well as mental retardation and epilepsy. Mutations in *GABRB3* are detected in epilepsy. Individuals with epilepsy tend to have more severe symptom when a deficiency of *UBE3A* is also present.<sup>125</sup> *GABRB3* is a major inhibitory neurotransmitter of the mammalian nervous system.

### Glutamate receptors

Glutamate (glutamic acid) is the main excitatory neurotransmitter in the mammalian central nervous system. It acts at a number of receptors, which are defined by the agonists that activate them. The receptors are classified as ligand-gated ion channels (ionotropic receptors) and G-protein-coupled (metabotropic) receptors.<sup>85</sup> Metabotropic receptors consist of Class I (mGluR1, 5), Class II (mGluR2, 3), and Class III (mGluR4, 6, 7, 8) receptors. Ionotropic receptors consist of AMPA (GluR1 to GluR4), kainate (GluR5 to GluR6),

NMDA (GluN1, GluN2A to GluN2D, and GluN3A to GluN3B) and Glu  $\delta$  receptors. The NMDA receptors have a high permeability for  $\text{Ca}^{2+}$  ion and a high affinity for glutamate. One of the major functions of glutamate receptors appears to modulate synaptic plasticity, a property of the brain that is believed to be vital for memory and learning. An increase in the number of ionotropic glutamate receptors on a postsynaptic cell may lead to long-term potentiation of that cell and a decrease may lead to long-term depression. Metabotropic glutamate receptors trigger postsynaptic protein synthesis, which modulates synaptic plasticity through second messenger systems.

The *GRIN2A* on 16p13.2 locus may have an important implication for diagnostic testing. In a target gene capture of 18 epilepsy-associated genes in 519 probands with epileptic encephalopathies (EE) with diverse epilepsy syndromes, three different genetic mutations (c1005-1C>T, p.Thr531Met, and Phe139Ilefs\*15) in *GRIN2A*, a NMDA subunit, were found in four probands and were segregated with their families, and all four probands presented with epilepsy-aphasia syndromes (EAS), accounting for 9% (4/44) of EE cases with EAS. However, the mutations were found neither in the rest of 475 EE cases nor in 6,500 control exomes.<sup>126</sup> The mutations in *GRIN2A* could be used for diagnosis testing for EE with EAS. A chromosomal translocation t(16;17) (p13.2;q11.2) involving *GRIN2A* was found in a family with epilepsy and neurodevelopmental defects. A novel de novo missense mutation in *GRIN2A* (c.2449A>G, p.Met817Val) is the likely cause of refractory epilepsy and global developmental delay.<sup>127</sup>

### Nonion channel gene mutations

In addition to the mutations in the ion channel genes, recently exome-sequencing study also showed that mutations in nonion channel genes are involved with the development of epilepsy. Some mutations such as *LGII*, *PRRT2*, *EFHC1*, *PRICKLE*, *RBFOX1*, and *DEPDC5* are found in individuals with a clear inheritance of epilepsy or with a specific phenotype (Table 3).

### LGII

The *LGII* gene is located at a linkage region on chromosome 10q24. Mutations in *LGII* are more prevalent in ADLTE, ADPEAF, or sporadic epilepsy.<sup>128</sup> More than two dozens of mutations have been detected with *LGII* in patients with ADLTE.<sup>129</sup> *LGII* mutations were found in seven out of 14 families with ADPEAF and are believed as a common cause of epilepsy.<sup>130</sup> The *LGII* encodes a member of the

secreted leucine-rich repeat (LRR) superfamily and shares homology with members of the SLIT protein family.

Two distinct molecular mechanisms may underlie ADLTE. The one recognizes LGI1 as a novel subunit of the presynaptic Kv1 potassium channel implicated in the regulation of channel inactivation, while the other suggests that LGI1 acts as a ligand that selectively binds to the postsynaptic receptor *ADAM22*, thereby regulating the glutamate–AMPA neurotransmission.<sup>131</sup> Both mechanisms imply that LGI1 mutations result in an alteration of synaptic currents.

## PRRT2

*PRRT2* encodes a transmembrane protein containing a proline-rich domain in its N-terminal half and is located at 16p11.2 microduplications implicated for epilepsies.<sup>61</sup> A whole-exome sequencing analysis of eight Han Chinese families with histories of paroxysmal kinesigenic dyskinesia (PKD) detected c.514\_517delTCTG (p.Ser172Argfs\*3) and c.972delA (p.Val325Serfs\*12) each in one individual family and c.649dupC (p.Arg217Profs\*8) in six families.<sup>132</sup> The truncating mutation c.649dupC in *PRRT2* is a hotspot mutation resulting in benign familial infantile epilepsy (BFIE) or infantile convulsions with paroxysmal choreoathetosis (ICCA) regardless of the ethnic background. A Japanese study found heterozygous truncated mutation c.649dupC in 15 of 26 individuals with benign infantile epilepsy (52.1%), and all three families of ICCA harbored the same mutation (100%).<sup>133</sup>

The *PRRT2* mutation appears to affect a spectrum of neurological disorders and is common to multiple racial groups, including Chinese, Japanese, and European ancestry populations, as well as African American family.<sup>134,135</sup> The mutation c.649\_650insC was found in five of six families affected with ICCA syndrome and in 14 of 17 families affected with BFIE,<sup>136</sup> and a majority of the sample was Australian with Western heritage. A mutation c.649delC is detected in a family with four people affected with different phenotypes of febrile convulsion, epileptic seizures, PKD, or a headache. However, in another study of 24 child probands with BFIE, convulsions with mild gastroenteritis, and benign early infantile epilepsy in Japanese families, the insertion mutation c.649\_650insC was found in five families.<sup>137</sup> Wang et al<sup>138</sup> identified c.649-650insC mutation in all patients of two Han Chinese families with benign familial infantile seizure.

Studies in mice suggest that *PRRT2* is predominantly expressed in brain and spinal cord in embryonic and post-natal stages. A recent study suggested that mutant *PRRT2* may affect glutamate signaling and glutamate receptor activity through interaction with *SNAP25*, resulting in the

increase of glutamate release and subsequent neuronal hyperexcitability.<sup>139</sup>

## EFHC1

*EFHC1* is located at 6p12-p11, and it encodes an EF-hand-containing calcium-binding protein, which plays a key role in calcium homeostasis. Five missense mutations in *EFHC1* were found in six unrelated families affected with JME, one of the most frequent forms of IGE, but none of these mutations were present in ~400 controls.<sup>140</sup> In all, 9% of consecutive JME cases from Mexico and Honduras clinics and 3% of clinic patients from Japan carry mutations in *Myoclonin1/EFHC1*.<sup>141</sup> *EFHC1* is shown to regulate cell division and neuronal migration during cortical development; and disruption of its functions may lead to JME.<sup>142</sup> A recent study showed that *EFHC1* may be involved in the regulation of Wnt signaling that plays a role in human neuronal development and may affect the development of epilepsy.<sup>143</sup>

## Prickle homolog 1 (PRICKLE1)

*PRICKLE1* encodes a nuclear receptor that may be a negative regulator of the Wnt/beta-catenin signaling pathway. A homozygous mutation in human *PRICKLE1* identified in three pedigrees causes an autosomal recessive progressive myoclonus epilepsy–ataxia syndrome.<sup>144</sup> The possible mechanisms are likely through disrupted motor neuron migration and neurite extension and affected neuronal positioning. *PRICKLE1* is expressed in brain regions implicated for epilepsy and ataxia in mice and human beings. Moreover, prickle-mediated calcium signaling might underlie prickle function in the nervous system, reduce calcium activation, and dysregulate calcium currents.<sup>145</sup>

## RNA-binding protein, fox-1 homolog 1 (RBFOX1) and RNA-binding protein, fox-1 homolog 3 (RBFOX3)

Mutations in *RBFOX1* on 16p13.3 and *RBFOX3* on 17q25.3 are detected in patients with epilepsy. In addition to two hemizygous deletions, a 365 kb deletion affecting two untranslated 59-terminal exons of *RBFOX1* and a 43 kb deletion spanning exon 3 of *RBFOX3* were identified. An exome-sequencing analysis of 242 patients with RE revealed novel frameshift mutation (p.A233Vfs\*74) and a hexanucleotide deletion (p.A299\_A300del) in *RBFOX1* and a novel nonsense mutation (p.Y287\*) in *RBFOX3*.<sup>146</sup> Moreover, five exon-disrupting *RBFOX1* deletions ranging from 68 to 896 kb affecting the untranslated 5'-terminal *RBFOX1* exons were detected in 1,408 patients with IGE, but not in 2,256 controls.<sup>147</sup>

The possible mechanism is that knockdown of *RBFOX1* transcripts in human neurons changes the alternative splicing pattern, and the expression of primarily neuronal genes involved in synapse formation and function that lead to an increased susceptibility for seizure events.<sup>148</sup> *RBFOX* and *PTBP1* proteins interacting together regulate the alternative splicing of microexons (<51 nucleotides) in human brain transcripts.<sup>149</sup> This may have important implications because *RBFOX* proteins are well known to play crucial roles in both brain development and function. Aberrant splicing induced by *RBFOX* dysregulation is associated with a variety of brain-related disorders, including autism, mental retardation, and epilepsy.<sup>150,151</sup>

## DEPDC5

*DEPDC5* is located on chromosome 22q12.2-q12.3, and it encodes a member of the IML1 family of proteins involved in G-protein signaling pathways. Mutations in *DEPDC5* are identified in 10 of 82 families with autosomal dominant familial with focal epilepsy with variable foci (FFEVF), suggesting a common cause for FFEVF.<sup>152</sup> Whole-exome sequencing analysis revealed a splice acceptor mutation (c.2355-2A>G) and three nonsense mutations (p.Arg487\*, p.Arg1087\*, and p.Trp1369\*) in *DEPDC5* in probands of 30 European families with ADNFLE.<sup>153</sup> In addition to a frameshift mutation in *DEPDC5* identified in a family with FFEVF, five additional mutations in *DEPDC5* are found in 15 families affected with a broad spectrum of focal epilepsies.<sup>154</sup> The mutations in *DEPDC5* are associated with both lesional and nonlesional epilepsies even within the same family.<sup>155</sup> At the clinical level, however, 78% of the patients with *DEPDC5* mutations are drug resistant.<sup>153</sup>

*DEPDC5* may have implications for a broad spectrum of familial focal epilepsies. Previous studies have linked ion channel subunit genes (eg, *CHRNA4*, *CHRNA2*, *CHRN2*, and *KCNT1*) to ADNFLE and neuronal-secreted protein (LG11-encoding epitempin) to ADPEAF. The mTORC1-repressor gene *DEPDC5* has recently been reported in multiple inherited focal epilepsies such as ADNFLE, FTLE, and FFEVF.<sup>156</sup> This suggests that *DEPDC5* may have broad implications for epilepsy syndrome.<sup>157</sup> *DEPDC5* negatively regulates the mammalian target of rapamycin (mTOR) pathway, which regulates cell growth by sensing the availability of nutrients.

Mutations in multiple other genes (eg, *CARS2*, *CLN6*, *COL6A2*, and *GOSR2*) are reported in patients with PME. A homozygous mutation (c.655G>A) in *CARS2* is confirmed in the family with PME.<sup>158</sup> This mutation is located at the

last nucleotide of exon 6, results in a removal of exon 6, and leads to an in-frame deletion of 28 amino acids in a conserved sequence motif of the protein involved in the stabilization of the acceptor end hairpin of tRNA. A whole exome-sequencing combined with homozygosity mapping identified mutations in *CLN6* associated with the teenage-onset PME.<sup>159</sup> The p.Asp215Asn mutation in *COL6A2* is identified in a consanguineous family with PME.<sup>160</sup> Mutations (c.430G>T, p.Gly144Trp) in *GOSR2*, a Golgi vesicle transport gene encoding a vesicle docking proteins, are identified in patients with PME.<sup>161</sup>

Lastly, a novel homozygous nonsense mutation in exon 11 (c.1270C>T) changing arginine to a premature stop codon (p.R424X) in *SCARB2* is found for epilepsy.<sup>162</sup> A loss-of-function mutation in *SCARB2* has been identified in families with the action myoclonus–renal failure syndrome, which is an autosomal recessive form of PME. This gene encodes a lysosomal integral membrane protein of 478 amino acids (IMP2), which is important for lysosomal mannose-6-phosphate-independent trafficking of  $\beta$ -glucocerebrosidase.

## Epigenetics of epilepsy

While numerous single mutations have been identified for epilepsy, they account for little of the heritability. Most of these mutations, especially those in the ion channel genes, are rare or not even found in the genomic database.<sup>84</sup> The heritability of epilepsy is estimated to be ~0.30, which is moderate and lower than most of the neurodevelopmental and neuropsychiatric disorders such as autism. Environmental factors alone or interacting with genetic variants may play some roles in the development of epilepsy. Epigenetic regulation is another mechanism through which environmental factors affect the development of epilepsy.

Epigenetics refers to “heritable” changes in gene expression or phenotype that do not involve changes to the underlying DNA sequence. However, sometimes researchers also seek to describe dynamic alterations in the transcriptional potential of a cell, which may not be heritable. Common epigenetic mechanisms include DNA methylation, post-translational histone modification, and non-coding RNA. These epigenetic processes determine not only gene expression or silencing but also where, when, and how gene are expressed and then which proteins are transcribed.<sup>163</sup> The epigenetic process is influenced by age; physical environments such as nutrients, smoking, drugs, and chemicals; and even psychosocial events such as stressful life events.

Epigenetics plays a role in neuronal function from embryogenesis and early brain development to tissue-specific

gene expression. Evidence has shown that micro-RNAs, one type of non-coding RNAs, modulate the translation of target genes in early stages of brain development and are critical to dendritogenesis, synapse formation, and maturation.<sup>164</sup> Therefore, dysregulation of epigenetics would have a significant role in neuropsychiatric disorders, including stroke and epilepsy, as well as other diseases such as cancer, autoimmune diseases, and diabetes.<sup>165</sup> Because epigenetic changes are reversible and such pathological epigenetic modifications are readily curable through pharmacological interventions, the epigenetic machinery may provide a new platform for therapeutic approaches against these diseases.<sup>166</sup>

## DNA methylation

Aberrant DNA methylation may contribute to the pathophysiology of epilepsy and other neurodevelopmental, neuropsychiatric, and neurodegenerative disorders. Using biopsy brain specimens from 16 adult patients with temporal lobe epilepsy (TLE) and autopsy brain samples from three age-matched controls, a study found hypermethylation at the reelin promoter in the dentate gyrus of TLE patients.<sup>167</sup> The aberrant DNA methylation may cause dispersion of granule cell and the deficiency in the reelin expression that are found in epilepsy. A genome-wide DNA methylation analysis of hippocampus in mice to define the pattern of status epilepticus and epileptic tolerance also showed that >300 genes showed altered DNA methylation, with 90% of the promoters of these genes undergoing hypomethylation.<sup>168</sup> The DNA methylation has been implicated in genome stability, silencing transposable element, and repressing gene expression that affects brain development, leading to multiple neurological disorders.<sup>169</sup> DNA methyltransferase (DNMT) enzymes catalyze DNA methylation and results in the formation of 5-methylcytosine, primarily at CpG dinucleotide-containing regulatory sequences. The role of DNA methylation in the pathogenesis of epileptic syndromes, including TLE, PWS, and AS, has already been elucidated by some studies.<sup>167-169</sup>

## Histone modification

Histone acetylation and phosphorylation are two most common processes of histone modification.<sup>170</sup> While histone hyperacetylation indicates an increase in gene activity, its hypoacetylation marks gene repression. The hyper- and hypo- methylation are controlled by a dynamic interplay of histone acetyltransferase (HAT) and histone deacetylase (HDAC). A study has shown that acetylation of histone H4 in rat hippocampal CA3 neurons is reduced at the promoter

of glutamate receptor 2 (GluR2, encoded by *GRIA2*) but increased at brain-derived neurotrophic factor (BDNF) promoter P2 as soon as 3 hours after induction of status epilepticus by pilocarpine.<sup>171</sup> In examining the effect of kainate-induced status epilepticus on two different histone modifications on histone H3 phosphorylation at serine 10 and histone H4 acetylation, a study demonstrated that histone modifications induced by kainate are involved not only in immediate early genes (IEGs) expression but also in the development of epilepsy.<sup>172</sup> Mutations in the histone demethylase KDM5C are linked to X-linked mental retardation and epilepsy.<sup>170-172</sup> Electroconvulsive seizures, produced by repetitive electronic stimulation, may lead to increased H4 acetylation at *c-fos* and *BDNF* gene promoters while decreasing at the *CREB* gene promoter in rat hippocampus.<sup>173</sup> *CREB* is a transcription factor that modulates the expression of the GABARs in the hippocampus and plays an important role in the epileptogenic process.

## Non-coding RNA

MicroRNA is a class of small non-coding RNA that plays a key role in epigenetic regulation by controlling the translation and/or stability of mRNAs, mainly via sequence-specific binding within the 3' untranslated region of mRNA transcripts. In human beings, there are ~1,600 miRNAs, which regulate more than half of protein coding genes, and each miRNA can regulate multiple proteins.<sup>174</sup> Because the brain expresses several unique miRNAs such as miR-34a that control dendritic morphology, ion channel level, neuronal migration, and glial function microRNA may have an important implication for neuropsychiatric disorders.<sup>175</sup> For example, miR-34a affected bipolar risk through directly impacting the *ANKK3* and *CACNB3* expressions,<sup>176</sup> and upregulation of miR-34a is associated with the risk of epilepsy.<sup>177</sup> miRNAs regulates neural differentiation, maintenance, and plasticity. Fragile X mental retardation protein (FMRP) results in epilepsy associated with Fragile X syndrome by glutaminergic and GABAergic synaptic dysfunctions at the mRNA and protein levels.<sup>175-177</sup>

In summarizing three independent epigenome-wide analyses of microRNA expression, Hwang et al<sup>164</sup> showed that miR-132 was consistently upregulated in the hippocampal CA3 in the rat animal model after status epilepticus. Five microRNAs, including miR-24, miR-29a, miR-99a, miR134, and miR375, are shown upregulated in at least two of three studies. However, no downregulated microRNA was consistently found across three studies. Because microRNAs tend to regulate multiple proteins and play a role

in neurodevelopment, they may hold promising for novel therapeutic development.

## Conclusion and future implication

Epilepsy is fundamentally a disorder of neuronal excitability, and its etiology is elusive. Genetic studies have indicated a number of single-point mutations in genes that involve voltage-gated sodium channels (*SCN1A*, *SCN1B*, *SCN2A*, and *SCN9A*), potassium channels (*KCNA1*, *KCNMA1*, *KCNMB3*, *LCN10*, *KCNQ2*, *KCNQ3*, and *KCNT1*), calcium channels (*CACNA1A*), ligand-gated GABARs (*GBAEA*, *GBARG2*, and *GABRB3*), glutamate receptors (*GRIN2A*), and acetylcholine receptors (*CHRNA2*, *CHRNA4*, and *CHRN2*). All of these are molecular mediators of excitability, and excitability molecules are predominant cellular components affected in epilepsies.<sup>178</sup> However, some of the genetic mutations identified in the ion channel genes are very rare and even hardly found in a normal population.

The genome-wide analysis also shows that CNVs and single-point mutations in nonion channel genes affect epilepsy. While epilepsy shares some common genetic lesions such as microdeletions at 15q11.2, some of them disrupt a few credible candidate genes such as *NRXN1*, *AUTS2*, *NLGN1*, *CNTNAP2*, *GRIN2A*, *PRRT2*, *NIPA2*, *BMP5*, and *PODXL* that have been implicated in other neurodevelopmental disorders, including intellectual disability, autism, and schizophrenia.<sup>179</sup> Recent exome-sequencing study of families with epilepsy revealed that mutations in some genes such as *LGII*, *PRRT2*, *EFHC1*, *SYNGAP1*, *PRICKLE1*, *RBFOX1*, *RBFOX3*, and *DEPDC5* may account for a certain proportion of familial epilepsy cases. Some mutations such as c.649\_650insC in *PRRT2* are present in a majority of families with probands of PKD, BFIE, and ICCA syndrome. Some of these genes strongly suggest that neurodevelopment was involved in the development of epilepsy.

While genetic study allows us to understand the etiology of epilepsy, it is likely that genetic variants only directly contribute to a proportion of the liability of epilepsy. Genome-wide association studies have only identified a few common variants associated with epilepsy through genome-wide association study. Given that the heritability of epilepsy is just moderate, environmental factors may contribute to the etiology of epilepsy.<sup>180</sup> So far, preeminent genetic variants that have been found in epilepsies are single-point mutations (de novo or inherited). The epigenetic mechanism may play a key role in interpreting how environmental factors cause the phenotype or phenotypic variations and how the DNA mutational variants may contribute to phenotypic traits.<sup>7,181</sup>

Epigenetic silencing may cause the loss of function of genes and predisposes to a genetic mutation. Genes controlling the cell cycle and DNA repair, such as *RB*, *BRCAl/2*, and *PTEN*, have all been reported to be hypermethylated or mutated/deleted in cancer. Promoter hypermethylation is the predominant mechanism for the loss of function of some genes.<sup>182</sup> Evidence has shown that altered epigenetics promote genome instability and formation of genetic mutations.<sup>183</sup> CpG DNA methylation may facilitate a C to T conversion, the most frequent point mutation. Translocation events and inversions are also influenced by histone modifications, DNA methylation, and ncRNA.<sup>182</sup> A recent study indicates that environmentally induced epigenetic transgenerational inheritance of disease and phenotypic variation can promote genetic mutations (ie, CNVs) in later generations.<sup>182</sup>

The future study of epilepsy should focus on integrating whole-genome sequencing variants and environmental factors into epigenetic change to understand the potential mechanism of epilepsy. Given that epigenetic regulation is tissue specific and may be susceptible to confounding factors, a careful design using systems biology approach that unifies genetics, environmental factors, epigenetic regulation, and gene expression will be required to understand the epigenetic mechanism of epilepsy. Family based samples allow us to effectively control for the potential genetic heterogeneity or population stratification that arises from the case–control study. The epigenetic study may also facilitate biomarker discovery and the potential development of novel therapeutics for epilepsy.

## Disclosure

The authors report no conflicts of interest in this work.

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