An advance about the genetic causes of epilepsy

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Abstract: Human hereditary epilepsy has been found related to ion channel mutations in voltage-gated channels (Na⁺, K⁺, Ca²⁺, Cl⁻), ligand gated channels (GABA receptors), and G-protein coupled receptors, such as Mass1. In addition, some transmembrane proteins or receptor genes, including PRRT2 and nAChR, and glucose transporter genes, such as GLUT1 and SLC2A1, are also about the onset of epilepsy. The discovery of these genetic defects has contributed greatly to our understanding of the pathology of epilepsy. This review focuses on introducing and summarizing epilepsy-associated genes and related findings in recent decades, pointing out related mutant genes that need to be further studied in the future.

1 Introduction

Epilepsy is a neurological disorder characterized by epileptic seizures caused by abnormal brain activity. 1 in 100 (50 million people) people are affected by symptoms of this disorder worldwide, with men, young children, and the elderly having a higher risk than adult women. The pathology of epilepsy is complex and diverse. Symptoms of epilepsy can range from having unusual behaviors, sensations, and temporary confusion to unprovoked seizures and uncontrollable jerking movements of the limbs.

Acquired and genetic factors both contribute to the etiology of most epilepsy. Although environmental factors are non-negligible, the main causes of epilepsy are still genetic factors.

There are over 50% of epilepsies have a genetic basis [1]. These genes may be a single gene, a specific group of genes, mutations in DNA [2]. Epileptic encephalopathy can be due to structural abnormalities in acquired related proteins, such as ion channels, or the mutations in specific genes that affect neuronal excitability. In fact, through advanced next-generation high-throughput sequencing technology, the current study has identified a number of novel candidate genes that may play a role in the pathogenesis of the early epileptic disease. Increased understanding of the genetic insights into these syndromes contributes to developing specific treatments for the clinic disease. To help us gain insight into the pathologic mechanisms, we will introduce the known epileptic-related genes, especially ion channels coding genes, and their different pathogenic mechanisms in the following article.

2 Malfunction of Ion channel

Functional variation in voltage or ligand-gated ion channel mutations is a major cause of idiopathic epilepsy, especially in rare genetic forms. Genetic analysis of different ion channels provides an important reason for the pathologic pathway from mutation to an epileptic seizure. The ion channel variations can also induce common epileptic disorders, such as juvenile myoclonic epilepsy or pediatric and adolescent deficiency epilepsy. These ion channels include the potassium channel, sodium channel, calcium channel, and calcium channel.

Table 1. Classification of ion channel genes associated with epilepsy mentioned in this paper

Related Ion Channel	Related Genes
sodium channel	<i>SCN1A, SCN2A, SCN3A, SCN8A, SCN9A</i>
calcium channel	<i>CACNA1A, CACNA1H, CACNA1G</i>
chloride channel	<i>CLCN4, CLCN6</i>
potassium channel	<i>KCNA2, KCNB1, KCNC1, KCNMA1, KCNQ2, KCNQ3, KCNT1</i>

Note: SCN1A, Sodium Voltage-Gated Channel Alpha Subunit 1; SCN2A, Sodium Voltage-Gated Channel Alpha Subunit 2; SCN3A, Sodium Voltage-Gated Channel Alpha Subunit 3; SCN8A, Sodium Voltage-Gated Channel Alpha Subunit 8; SCN9A, Sodium Voltage-Gated Channel Alpha Subunit 9; CACNA1A, Calcium Voltage-Gated Channel Subunit Alpha1 A; CACNA1H, Calcium Voltage-Gated Channel Subunit Alpha1 H; CACNA1G, Calcium Voltage-Gated Channel Subunit Alpha1 G; CLCN4, Chloride Voltage-Gated Channel 4; CLCN6, Chloride Voltage-Gated Channel 6; KCNA2, Potassium Voltage-Gated Channel Subfamily A Member 2; KCNB1, Potassium Voltage-Gated Channel Subfamily B Member 1; KCNC1, Potassium Voltage-Gated Channel Subfamily C Member 1; KCNMA1, Potassium Calcium-Activated Channel Subfamily M Alpha 1; KCNQ2, Potassium Voltage-Gated Channel Subfamily Q Member 2; KCNQ3, Potassium Voltage-Gated Channel Subfamily Q Member 3; KCNT1, Potassium Sodium-Activated Channel Subfamily T Member 1.

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2.1 Mutation of potassium channel

Among all K⁺ channel families, the Kv family (voltage-gated K channel) in the K⁺ channel family is considered the most related family with human epilepsy [3]. There are approximately 40 types of genes encoding for the Kv family, and 12 of them are strongly implicated in epilepsy [4,5]. The potassium voltage-gated channel subfamily A member 1 (KCNA1) gene codes for the Kv1.1 subunit on the axonal membrane and presynaptic nerve terminals contribute to membrane repolarization and formation of action potentials. Common mutations in the KCNA1 gene can cause episodic ataxia type 1 (EA1), a neuronal channelopathy marked by brief episodes of cerebellar instability and chronic neuromyotonia [6-8]. Moreover, there are potassium voltage-gated channel subfamily Q member 2 and member 3 (KCNQ2&KCNQ3) genes highly expressed in the brain, mostly in the hippocampus, temporal cortex, cerebellar cortex, and medulla oblongata. The mutations in KCNQ2 and KCNQ3 genes were identified to be associated with Benign familial neonatal seizures (BFNS) [9,10].

Table 2. Kv channels and their related genes.

Kv Family		
Channels(α -subunits)	Gene names	Other names
Kv1.1-Kv1.8	<i>KCNA1-7,10</i>	Shaker
Kv2.1-Kv2.2	<i>KCNB1-2</i>	Shab-related
Kv3.1-Kv3.4	<i>KCNC1-4</i>	Shaw-related
Kv4.1-Kv4.3	<i>KCND1-3</i>	Shal-related
Kv5.1	<i>KCNF1</i>	Modifier
Kv6.1, Kv6.4	<i>KCNGL1,4</i>	Modifiers
Kv7.1-Kv7.5	<i>KCNQ1-5</i>	Modifiers
Kv8.2	<i>KCNV2</i>	Modifier
Kv9.1-Kv9.3	<i>KCNS1-3</i>	Modifiers
Kv10.1-Kv10.2	<i>KCNH1,5</i>	Eag1-3
Kv11.1-Kv11.3	<i>KCNH2,6,7</i>	Erg1,2
Kv12.1-Kv12.3	<i>KCNH8,3,4</i>	Elk1-3

2.2 Mutation of sodium channel

Voltage-gated sodium channels (NaV) mainly exist in the central nervous system (CNS), Peripheral nervous system (PNS), skeletal muscle, and cardiac muscle, which are responsible for the initiation and propagation of action potentials in excitable cells. Among the nine different α subtypes of NAV (Nav1.1-Nav1.9) that have been studied, SCN1A(Nav1.1), SCN2A(Nav1.2), SCN3A(Nav1.3), SCN8A(Nav1.6), and SCN9A(Nav1.7) are gene mutations associated with channel lesions that ultimately lead to epilepsy [11,12].

SCN1A gene codes for the α subunit of the Nav1.1 sodium channel are expressed widely in CNS to inhibit GABAergic interneurons and control neuronal excitability. The mutation causes a decrease in the ion channel activity and further leads to epilepsy due to the imbalance between inhibition and excitation. Epilepsy associated with problems with the SCN1A gene includes febrile seizures and severe myoclonic epilepsy (SMEI)

[13-15]. The NaV1.2 subunit is encoded by the SCN2A gene. Unlike the NaV1.1 channel, the SCN2A gene is highly expressed in the GABAergic interneurons. More than 100 mutations in the SCN2A gene have been discovered. West syndrome, epilepsy of infancy with migrating focal seizures, and benign hereditary neonatal-infantile seizures are the most common diseases associated with SCN2A mutation [16,17]. SCN3A gene encodes for the alpha subunit of NaV1.3 and it is in a cluster with SCN1A and SCN2A. Studies showed that nervous system injury and neuropathic pain have an increasing presence of NaV1.3 channels in affected tissues, related to hyperexcitability of sensory neurons associated with pain [18]. One report from Katherine D showed that a new coding variant, SCN3A-K354Q, was considered to cause the increase in persistent current that is similar in magnitude to epileptogenic mutations of SCN1A and SCN2A [19].

The SCN8A gene and the SCN9A gene encode for voltage-gated Na⁺ channel alpha subunit in Nav1.6 and Nav1.7. Nav1.6 channel is abundant in the Ranvier nodes of myelinated axons and the distal portion of the axon initial segments (AIS), a specialized membrane area in neurons that activates action potentials in humans. SCN8A mutations cause the overexpression of Nav1.6 in the AIS and an increase in random and repetitive firing linked to early-infantile epileptic encephalopathy type 1a (DEE1). For the SCN9A gene, mutations in this channel contribute to pain disorders with the gain of function (GOF) and the loss of function (LoF), which are related to erythromelalgia (EMI), small-fiber neuropathy (SFN), and congenital insensitivity to pain (CIP) [20-22].

Table 3. Sodium channels related genes and its related epilepsy symptoms.

Mutation of sodium ion channel coding gene	
Gene name	Related epilepsy symptoms
<i>SCN1A</i>	Febrile seizures, severe myoclonic epilepsy (SMEI)
<i>SCN2A</i>	West syndrome, migrating focal seizures, benign hereditary neonatal-infantile seizures
<i>SCN3A</i>	Possible early childhood epilepsy
<i>SCN8A</i>	early-infantile epileptic encephalopathy type 1a (DEE1)
<i>SCN9A</i>	erythromelalgia (EMI), small-fiber neuropathy (SFN), congenital insensitivity to pain (CIP)

2.3 Mutation of calcium channel

Calcium channels are present in most excitable cells. They can provide appropriate voltage conditions for the occurrence of potassium current, chloride current, and sodium-calcium exchange current in the membrane of excitable cells. Since Ca²⁺ is a key factor in the regulation of cell proliferation, migration, phagocytosis, and secretion of inflammatory mediators, calcium ion channels are vital in the excitability of neurons and regulation of the shape and duration of action potentials, and even in other types of cells, such as immune cells, blood cells and sperm cells [23,24]. Calcium channels can be mainly divided into three types: voltage gated calcium channels (VGCCs), receptor-operated calcium channels,

and other calcium channels. This paper will mainly introduce epilepsy caused by the mutation in VGCCs.

VGCCs can be divided into three types: Cav1, Cav2, Cav3. All these channels consist of these subunits: α_1 , $\alpha_2\delta$, β_1 -4, and γ . There are 10 gene encodes for these channels (Fig. 1). However, only three genes have been shown in OMIM to cause epilepsy after variants: CACNA1A, CACNA1H, CACNB4[25]. According to the present study, the gene that is absolutely associated with epilepsy is CACNA1A and other genes, including CACNA1G, CACNA2D1, CACNA2D2, RYR3, and TRPM1, are potential epilepsy-related genes [25,26].

Fig. 1. Classification of calcium channels [27]. HVA, high voltage activated; LVA, low voltage activated. VGCCs can be divided into two types: HVA and LVA. HVA includes Cav1 channels (L-type channels) and Cav2 channels (including P/Q-type channels, N-type channels, and R-type channels). LVA includes Cav3 channels (which are T-type channels).

Table 4. Three epilepsy related genes introduced in this paper [28]

α_1 -Subunit Gene	α_1 -Subunit	channelopathies (OMIM)
CACNA1A	Cav2.1 (P/Q-Type)	Familial and Sporadic Hemiplegic Migraine Type 1 with or without progressive cerebellar ataxia (#141500, AD, DN)
		Episodic Ataxia Type 2 (#300071, XL)
		Spinocerebellar Ataxia Type 6 (#183086, AD)
		Early Infantile Epileptic Encephalopathy 42 (#617106, AD)
		Congenital Ataxia*
CACNA1G	Cav3.1	Spinocerebellar Ataxia Type 42 (#616759, AD)
		Spinocerebellar Ataxia Type 42 early-onset, with neurodevelopmental deficits (Childhood-Onset Cerebellar Atrophy; #618087, AD)
		Familial Hyperaldosteronism type IV (#617027, AD)
CACNA1H	Cav3.2	Aldosterone producing adenomas (APAs, somatic, DN)

Note: This table lists CACNA1A, CACNA1G, CACNA1H, their corresponding protein, and channelopathies shown in OMIM

CACNA1A encodes Cav2.1 channel, which conducts P/Q type channel Ca^{2+} currents and adjusts the motor functions and regulates brain rhythmogenesis [29]. In humans, mutations in CACNA1A have been most strongly associated with ataxia, migraine, and absence epilepsy [26,30]. Absence epilepsy is mainly related to thalamocortical oscillations, in which Cav2.1 plays an important role [31]. Miao et al. also proved that mutation

in the P/Q type channel could cause epilepsy and ataxia through loss-of-function experiments [29]. So, there is strong evidence that mutation in CACNA1A is one of the reasons causing epilepsy.

Cav3 channels (also known as low-voltage-activated channels or T-type Ca^{2+} channels) exist in neuron systems widely [32]. Mutations in the genes encoding Cav3 channels like CACNA1G and CACNA1H are more likely to develop epilepsy than that of CAV2 channels, especially absence epilepsy [33-35]. Many scholars proved that variations in CACNA1G exacerbate symptoms caused by mutations in the SCN2A gene can also cause spinal cerebellar ataxia (SCA)-induced epilepsy [36-40]. So, from the present study and observation, mutations in CACNA1G can lead to variation in SCN2A, causing epileptic symptoms by SCA.

The gene CACNA1H encodes the α_1 pore-forming subunit of Cav3.2 [41]. However, it remains ambiguous whether CACNA1H variants are a cause of monogenic epilepsy or not. Some scholars hold the opinion that it's not the reason for epilepsy. Jeffery et al. proved that compared with some antiepileptic drugs, the magnitude of the effect caused by the mutation in CACNA1H is not strong enough [42]. Kenneth et al. suggest that variants in CACNA1H predict little response to ETX [43]. Also, exome sequencing of common epilepsies fails to detect CACNA1H [39,42]. However, other researchers hold quite different views. Qing-Long Miao et al. prove CACNA1H gene loss-of-function in a seizure model [29]. Ivana A. Souza Et al. reported a child with primary generalized epilepsy caused by variants in CACNA1H [41]. Therefore, whether CACNA1H can cause epilepsy is controversial.

2.4 Mutation of Chloride channel

Along with Na^+ , K^+ , Ca^{2+} ion channels, mutations that cause dysfunctions in Cl^- channels are also shown to be associated with various forms of generalized epilepsy [44]. GABAA receptor is the inhibitory neurotransmitter receptor with a central Cl^- permeable pore that controls inhibition in the basal ganglia [45]. When two GABA molecules bind to the extracellular receptor domain, a conformational change occurs in the oligomer, which causes Cl^- to move into the cell, inducing inhibitory hyperpolarization of the neuron [45]. Several different inherited epilepsy synonyms are due to the altered composition of GABAA receptor subunit genes caused by genetic variations, including GABRA1, GABRB3, GABRD, and GABRG2. The keys of GABAA-receptor related variants are to depolarize signaling due to the inability of newborn neurons and maintain intracellular low chloride ions. The effects of specific mutations on GABA receptor function include reduced current, reduced single-channel opening time, and accelerated whole-cell electrical loss and activation. It likely result in a range of disorders, including early infantile epileptic encephalopathy (EIEE) and global epilepsy with fever (GEFS+).

A susceptibility locus for common idiopathic generalized epilepsies (IGE) syndromes is a gene called

SLC4A3, which is in chromosomal region 2q36. SLC4A3 is a gene that encodes for the anion exchanger isoform 3. It is expressed prominently in the brain, and its function mainly includes inducing electroneutral exchange of chloride and bicarbonate [46]. CLCN2 is another Cl⁻ channel gene associated with epilepsy. CLCN2 encodes for the ClC-2 Cl⁻ channel, which is also widely expressed in the brain. It is essential for GABA-mediated inhibition and maintenance of low intracellular Cl⁻ concentration [44]. A study by Scheffer & Berkovic [44] indicated a relationship between heterozygous mutations of CLCN2 and idiopathic generalized epilepsies. These mutations may cause impaired Cl⁻ efflux, resulting in the accumulation of Cl⁻ in the intracellular space and further decreasing the transmembrane gradient Cl⁻, which reduces the inhibitory GABA-mediated response. Specifically, these mutations may result in a premature stop codon, atypical splicing, or a single amino-acid substitution [47]. Most mutations produce functional alterations that explain their pathogenic phenotypes. A premature stop codon and atypical splicing may cause a loss of function (LoF) of the ClC-2 channels and lower the transmembrane chloride gradient essential for GABAergic inhibition. The single amino-acid substitution may act to alter voltage-dependent gating, which may cause membrane depolarization and hyperexcitability [47].

3 Mutation of Acetylcholine receptor gene

Neuronal nicotinic acetylcholine receptor (nAChR) is a pentameric ion channel formed by the combination of various α and β subunits, which determines the characteristics of different functions of each subunit. Mutations in the α -4 (CHRNA4), β -2 (CHRN2), and α -2 (CHRNA2) subunits of the nAChR are associated with certain kind of epilepsy like autosomal dominant nocturnal frontal lobe epilepsy and familial sleep-associated hypermotor epilepsy (known as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [48]. Most of these mutations are found in the CHRNA4 and CHRN2 genes because of the prevalence of the α 4 and β 2 subtype in the mammalian brain, resulting in clusters of brief motor traits that occur mostly during non-REM sleep, resulting in epilepsy occurring [49].

Neuronal nicotinic acetylcholine receptor α 4 subunit (CHRNA4) is localized in the same region of 20q and expressed in all the frontal cortex layers. Missense mutations in the α 4 subunit of nAChR can alter the function of NACHR, associated with autosomal dominant nocturnal frontal lobe epilepsy [50]. For example, serine substitution for phenylalanine on codon 248, a highly conserved amino acid residue in the second transmembrane domain, has been found. It may result in reduced protein secretion levels in the short time, thus suggesting that mutated people could present an altered capability to respond immediately to stress agents [50].

The CHRN2 mutation I312M that has been studied is located in the outer transmembrane region 3 (M3) of the

known ADNFLE mutation cluster and significantly increases the receptor's sensitivity to acetylcholine [51]. Phenotypically, this mutation is associated with both typical ADNFLE and obvious memory deficits, which leads to cognitive problems in organizing and storing linguistic information [52].

4 Mutation of MTTL1 and MTTK

Abnormality of the transfer RNA mitochondrial leucine gene (MTTL1) and transfer RNA mitochondrial lysine gene (MTTK) can also lead to epilepsy. MTTL1 and MTTK mutations are the most common reasons for mitochondrial encephalomyopathy, accounting for about 80% of mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), and myoclonic epilepsy with ragged-red fibers (MERRF) cases [53], respectively. The MTTL1 gene provides instructions for producing a specific form of tRNA designated tRNA LEU (UUR), which helps assemble amino acids into protein proteins. During protein assembly, this molecule binds to the amino acid leucine (Leu) and inserts it into the proper place of the growing protein. Mutations in this gene like MTTL1 A3243G can alter the structure, stability, methylation, and aminoacylation, or codon recognition properties of mitochondrial DNA3. In this situation, the mRNA codon mismatch with the mutated tRNA anticodon, leading to inaccurate tRNA processing, which negatively affects the translation process and reduces the rate of protein synthesis and enzyme activity [54]. The MT-TK gene is designated as tRNA lys. This molecule attaches to lysine (Lys) and inserts it into the protein. Mutation in the MTTK gene by the mitochondrial tRNA encoding lysine may cause myoclonic epilepsy or red fiber tear syndrome, a maternal-inherited progressive mitochondrial encephalomyopathy.

5 Mutation of LGI1

Leucine-rich, glioma-inactivated one gene (LGI1) is a monogenic, human epilepsy-related gene that encodes a secreted neuronal protein. The mutation of LGI1 is associated with autosomal dominant partial epilepsy (ADPEAF) [55], a rare hereditary epilepsy syndrome characterized by partial seizures accompanied by auditory or visual hallucinations [56]. Many LGI1 mutations have been found to block the secretion of LGI1 in cultured cells in ADPEAF patients, and insufficient haploidy of LGI1 may be the cause of LGI1-mediated ADPEAF [57,58]. Research in 2013 focused on the role of autoantibodies to LGI1 associated with limbic encephalitis (LE) revealed some part of the molecular mechanism of LGI1 that results in abnormal brain excitability. The study explains that the discovered LGI1 antibody ADAM22 and the extracellular domain of soluble ADAM22 disrupted the interaction of LGI1-ADAM22 to reduce the synaptic AMPA receptor in rat hippocampal neurons. The study concluded that the genetic or acquired loss of LGI1-ADAM22 interaction would reduce AMPA receptor function and lead to epilepsy [59].

6 Mutation of POLG

Polymerase γ is a DNA polymerase responsible for the replication and repair of mitochondrial DNA [60]. Mutations in DNA Polymerase Gamma, Catalytic Subunit (POLG) cause secondary mtDNA damage and increased load of point mutations, which is usually considered to be a common manifestation of mitochondrial diseases [61,62]. POLG defection shows the current understanding of the mechanism in POLG-related epilepsy. A defective POLG would lead to mtDNA depletion, which subsequently causes the loss in complex 1 and intensifies mtDNA mutations' impact. Both complex 1 loss and mtDNA mutation will be the reason for the progressive loss of respiratory chain activity and finally causes a critical neuronal energy level triggering epilepsy or focal necrosis [63]. According to several research, the frequency of epilepsy in patients with mitochondrial disease show seizures is 35–60%. Based on a clinical review, 84% of cases among 372 patients who had POLG-related epilepsy harbored at least one of these pathogenic variants: P. ALA467THR, P. Trp748ser, and P. Gly848Ser. It is enough to show the importance of POLG in chronic disease [64].

7 Mutation of MASS1

All mutated genes associated with hereditary idiopathic epilepsies were thought to be due to ion channel subunits' deficiencies until recently [65]. An exception is the monogenic audiogenic seizure-susceptible (MASS1) gene, which is found to be associated with audiogenic epilepsy in the Frings mouse model [65]. A study by Nakayama et al. suggests that a loss-of-function mutation in MASS1 may cause seizure phenotypes. However, it is not likely that MASS1 contributed to the cause of febrile seizures [66]. Additionally, a study by Deprez et al. also determined a region in chromosome 5q14.3-q23.1 that is overlapped with a locus for febrile seizures (FEB4) where MASS1 was the disease gene [67]. Though, mutation analysis of the exons and exon-intron boundaries of MASS1 in the family did not reveal a disease-causing mutation [67].

8 Mutation of EFHC1

Mutation in EF-hand motif-containing protein (EFHC1) causes juvenile myoclonic epilepsy (JME) though inducing neuronal apoptosis [68]. A study by Katano et al. proved that EFHC1 regulates the activity of TRPM2. TRPM2 and EFHC1 are proteins that are co-expressed in hippocampal neurons and ventricle cells. Co-expression of EFHC1 significantly potentiates Ca^{2+} responses and cationic currents via recombinant TRPM2 in HEK293 cells. Furthermore, EFHC1 enhances TRPM2-conferred susceptibility of HEK293 cells to H_2O_2 -induced cell death, which is reversed by JME mutations, suggesting that TRPM2 contributes to JME phenotypes by mediating disruptive effects of JME mutations of EFHC1 on biological processes, including cell death [68].

Additionally, four missense mutations in Myoclonin1/EFHC1 of chromosome 6p12.1 were identified in 2004 in 20% of Hispanic families with Juvenile myoclonic epilepsy in a study by Medina et al. [69]. Furthermore, a study by Stogmann et al. sequenced 61 with idiopathic generalized epilepsy (IGE) syndromes for mutations in the EFHC1 gene [70]. This study suggests that EFHC1 mutations may underlie different types of epilepsy syndromes.

9 MUTATION OF GLUT1 AND SLC2A1

Familial glucose transporter type 1 (GLUT1) is a glucose transporter encoded by the gene SLC2A1. The deficiency of this transporter due to autosomal dominant inheritance of SLC2A1 mutations is linked to epilepsy [71]. Mutation in SLC2A1 leads to reduced protein function in which was found in 12% of patients with early-onset absence epilepsy [72]. The study by Suls et al. suggests that GLUT1 deficiency greatly contributes to the onset of early-onset absence epilepsy and that a ketogenic diet is effective in treating GLUT1 deficiency [73]. Another study by Striano et al. screened the SLC2A1 gene for mutations in a group of 95 European patients with familial idiopathic generalized epilepsies (IGE) [72]. This study concluded that defects in GLUT1 are a rare cause of IGE.

10 Mutation of ALDH7A1

Aldehyde Dehydrogenase 7 Family Member A1 (ALDH7A1) is used to encode the A1 gene in the aldehyde dehydrogenase 7 families associated with Pyridoxine-dependent epilepsy (PDE), a rare neurometabolic disorder accompanied by neonatal seizures. For instance, pyridoxine-dependent epilepsy is caused by a biallelic variant of the ALDH7A1 gene. This results in significantly elevated levels of α -amino hexanediol (α -AASA) in urine and plasma. Excessive accumulation leads to the inactivation of pyridoxal phosphate (PLP). In addition, the pathogenic ALDH7A1 variant can also cause folate-responsive epileptic seizures [74].

11 Mutation of PRRT2

The proline-rich transmembrane protein 2 gene (PRRT2) is the most common genetic cause of benign inherited epilepsy in infants. Mutations in PRRT2 are related to both epilepsy and movement disorders [75]. PRRT2 is associated with a genetic movement disorder known as paroxysmal motor dyskinesia (PKD), like convulsions with dancing stiffness in infants. Single recurrent mutations in PRRT2 account for nearly 80% of cases [75].

12 Conclusion

This review mainly explores ion channel genes (Na^+ , K^+ , Ca^{2+} , Cl^-), GABA receptor gene, and other genes that may lead to the occurrence of different epileptic diseases due to the gene variation. Many pathogenesis mechanisms

and mutation genotypes of epilepsy have been discovered. In the meanwhile, many questions concerning the basic mechanisms of epilepsy still cannot be answered currently. For instance, whether CACNA1H variants are a cause of monogenic epilepsy or not is still remains ambiguous. Some scholars believe that the effect caused by the mutation in CACNA1H is not strong enough to cause seizure disorder compared with some antiepileptic drugs [42]. In addition, studies have shown that some gene regulatory elements, such as repressor element 1-silencing transcription factor (REST), also have a greater likelihood of causing seizure disorder, not just variations that directly affect genes. Neuropathology for epilepsy needs to be further studied to improve our understanding of the causes for various kinds of epilepsy.

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