Rajkumar Prabhakaran[1], Meenakshi Sundari Rajendran[2,3,4], and Poornima Kannappan[2,3,4]

[1]Affiliation not available
[2]Department of Biochemistry, Karpagam Academy of Higher Education
[3]Tamil Nadu
[4]Department of Biochemistry, Karpagam Academy of Higher Education, Manonmaniam Sundaranar University

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Meenakshi Sundari Rajendran[1]*, Raj Kumar Prabhakaran[2], Poornima Kannappan[1]***

* Department of Biochemistry, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India.

** Manonmaniam Sundaranar University, Tirunelveli, Tamilnadu, India.

Email: biochemmeenakshi@gmail.com;poorniovya@gmail.com

Correspondence address: Department of Biochemistry, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India.

Abstract

Neurons are the basic cell structure of the nervous system and responsible for the communication between brain and body. Brain networks are formed from a single neuron to highly complexed interconnected ([?] 100 billion) neurons. Imbalances between excitation and inhibition mechanism of neuronal cells leads to altered brain network causing seizure/epileptic activity. The mechanism is known as an ictogenic mechanism. In particular, epilepsy is characterized by abnormal neuronal cells and several genetic factors are attributed for their development.*CHRNA4* is the first epileptic gene discovered in an autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Since, the era of epileptic genetics has reached to peaks and still extending the branches to study in detail to solve the mysteries behind the brain and epileptic/seizure genes. However, genes such as *AQP4, SESN3, ARX, NTNG1, NTNG2, TSC1 and TSC2* need more attention in epilepsy genetic studies. Therefore, this review describes brain network during epilepsy (recurrent seizure) as well as deals with recent studies on molecular genetics and identification methods of epilepsy.

Key words:

Brain network, epilepsy, ictogenic mechanism, molecular genetics, and neurons.

Introduction

Neurons are the basic cell structure of the nervous system. They are responsible for communication between brain and different parts of the body. The neuron which pass the signal is called as Presynaptic neurons and that which receives the signal is called as postsynaptic neurons. A neuron contains a cell body called as soma; a slender long projection responsible for conducting electric impulses known as an axon, tree like structures that receives the signals are dendrites, a gap between an axon and dendrite is called as synaptic cleft and the junction of neurons is synapses. Donald Hebb (neuroscientist) in 1949 proposed that "simultaneous activation of cells leads to pronounced increase in synaptic strength between those cells" a theory that is widely accepted today. In other words Hebbian theory says that "cells that fire together wire together," that forms the foundation of neural network study of the neurobiologist and scientist to find evidences of neuronal plasticity and modifications in neural network [1]. Brain networks are formed from

a single neurons to highly complexed interconnected ([?] 100 billion) neurons and which accounts for the physiolocal functional mechanism [2]. In 1871 a German anatomist Joseph von Gerlach postulated an obsolete scientific theory in neurobiology called Reticular theory stated that "everything in the nervous system, such as brain, is a single continuous network" and the theory was popularised by Camillo Golgi [3]. But later the theory was refuted by Santiago Ramón y Cajal using a staining technique discovered by Golgi [4], and showed that nervous tissue, like other tissues, is made of discrete cells and this led to the neuron doctrine concept [5] . Epilepsy characterised by recurrent, unprovoked seizure in the brain due to excessive action potential and synchronisation of the neurons. Whereas seizure can be defined as a temporary disturbance in the signal transduction of the brain in brief. Etiology of seizure includes genetic factors, loss of neuronal communications due to network instabilities, neuronal degenerations. Association with other neuronal syndromes like autism, loss of neuronal connectivity in neuronal ceroid lipofuscinoses or neurodegenerative diseases like Alzheimer's or Parkinson's disease, are some of the diseases showing epilepsy/seizure. Classification of epilepsy (see Figure: 1 schematic representation): 1. GGE 2. FE 3. EE.

GGE: Otherwise known as idiopathic generalized epilepsy. This involves both sides of the brain. Individuals with GGEs are intellect and normal. Epileptic symptoms may occur in any stages of life. (e.g.)Juvenile myoclonic epilepsy (JME) and childhood absence epilepsy (CAE).**FE:** As the name itself says, the origin of seizure is focused at one particular region of brain. e.g., include temporal lobe epilepsy (TLE), autosomal dominant epilepsy with auditory features and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [6].**EE:** In EEs developmental delay or regression associated with ongoing epileptic activity, characterized by refractory seizures, occurs in early onset conditions. West syndromes, Ohtahara and Dravetare well-studied EEs. Importantly, epilepsy is often a co-morbid condition in individuals with intellectual disability (ID), autism or schizophrenia and may be a feature of many metabolic conditions and genetic syndromes [6].

This review is aimed to summarize the changes occurring in the brain's electrochemical signals and the ictogenic mechanism of brain network. Additionally, current review discussed about the recent methods applied for the study of the novel epileptic genes and their role in an etiology of epilepsy as well as discuss about the molecular mechanism behind the voltage dripping in the neurons leading to epilepsy or seizure.

Brain's electrochemical network Brain can produce electrical and chemical signals. Electrical signals/activity of the brain can be displayed in form of brain waves, which ranges from the most active wave (gamma) to the least active wave (delta).There are five type of brain waves recorded through Electroencephalogram (EEG) namely alpha, beta, theta, gamma and delta. The frequency bands of α, β, ϑ, γ and δ were recorded in EEG (Table1) and their frequency ranges and brain states were clearly defined by the researchers [7]. A recent study in patients with cingulated gyrus epilepsy had identified the default mode network connectivity by magneto encephalography, and found significantly greater connectivity in three frequency bands (α, β, γ) compared to controls and the study reports showed greater functional connectivity in the γ band was significantly more prominent than that of the α and β bands in the patients with cingulated gyrus epilepsy [8]. In other study in patients with epilepsy (PWE), reveals that alpha band slowing and exteriorization occurs [9].Neuronal cells secretes neurotransmitter, which may have excitatory or inhibitory actions. Pre-synaptic neuron releases the neurotransmitter, which acts on the postsynaptic receptors, so that communication will result in either excitation or inhibition of postsynaptic neuron. This is the continuous process where the release of signalling molecules in the neuronal network communication occurs in the brain. Glutamate, gamma amino butyric acid (GABA), acetylcholine (ACh), histamine and hormones such as nor epinephrine, dopamine, serotonin, and are the major neurotransmitters of the brain; hormones and neuropeptides have the modulatory effects in the chemical signalling process for a longer time period. $Ca2^{+}$, Na^{+}, K^{+}, Cl^{-} are the important ions involved in neurotransmission. Voltage gated ion channels are the crucial one in the transmission of electrical potential, which is central to electrical signalling in neurons. By blocking synaptic and voltage-gated inhibitory conductance [10, 11] or by activating synaptic and voltage-gated excitatory conductance [12] an acute epilepsy can be induced.

Ictogenic mechanism of epilepsy vs seizure

An imbalance between excitation and inhibition mechanism will lead to normal brain network activity to

seizure/epileptic activity in the brain network. This is called as an ictogenic mechanism [13]. Involves "an activity dependent disinhibition" or "just reduction in the efficacy of activity dependent neuronal inhibition"[14,15,16].

Our brain as a huge network, continuously sending signals and when this network dynamics dominated by positive feedback mechanism of activity dependent disinhibition, the network activity of episodic surges in the brain may cross the seizure threshold. This would lead to degrade inhibition mechanism in an epileptic network, thus increases the brain activity and causes seizure [17].

When there is a reduction in an activity dependent inhibition, the brain network will be imbalanced by inhibition and excitation levels, and the excitation is higher. This produces seizure and continues to either enhancing excitation or by suppressing inhibition, providing the necessary feedbacks to sustain seizure [17].

Ictogenic mechanism of "epilepsy" is different from seizure during toxic exposure and an acutely induced seizure. By blocking or by activating, inhibitory and excitatory signals of voltage-gated channels and synaptic conductance epileptic activity can be induced [18, 19]. In case of seizure ictogenic mechanism occurs by increasing inhibition or decreasing excitation of signal occurs. An example of this type is Domoic acid activate GLUK1 excitatory glutamate receptors and theophylline overdose exposure mediated in inhibitory action in adenosine A1 receptors [20,21].

In human's vast majority of seizures are chronic rather than an acute toxic exposures, they are based on two different explanations: 1. Timing of seizure 2. Etiology of seizure.

Timing of seizure is unpredictable in chronic epilepsy and rare in seizures [22]. In chronic epilepsy, an ictogenic mechanism and an additional mechanism are required to explain the timing of episodic transitions from normal brain network to seizure activity. Stereotypic duration observed in both experimental and human seizure types and the timing ranges seconds to minutes. e.g., Absence epilepsy occurs in seconds and 1? and 2? generalised tonic clonic seizures occurs in minutes [23,24]. State of brain network is an important determinant of timing in seizure. e.g., Catamenial epilepsy depends on brain network state and occurs only during menstrual cycle and they don't explain seizure timing directly [25].

Trauma / head injury is one of the main causes for acquired epilepsy and it is very spontaneous. Stroke also has known etiology of epileptic seizures. Infection in the brain also sometimes leads to seizure. Among these various aetiologies, in this review we will be focusing on the genetic factors of epilepsy dealing with the molecular mechanism and their association in different seizure types.

In 1994, CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE (CHRNA4) is the first epileptic gene discovered in Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [26], since then the era of epileptic genetics has reached to peaks and still extending the branches to study in detail to solve the mysteries behind the brain and epileptic/seizure genes. Gene size, frequency, inheritance pattern, magnitude of effect, and phenotypic specificity are the genetic variants that influence epilepsy. Next-generation sequencing, novel epilepsy syndromes, and a greater integration of genetics into clinical decision making for individual patients are setting new trends and are emerging in epilepsy genetics.

Trending methods and molecular mechanism of novel gene studies

The frequency of epilepsy in relatives of individuals with epilepsy, at robust estimated for the overall risk was increased 3.3-fold by the age of 40, with a higher increase in risk for idiopathic/genetic generalized epilepsies compared to focal epilepsies, has been showed in an analysis of the Rochester Epidemiology Project [27]. Missing heritability is trending in molecular genetics to study only a small proportion of the overall genetic risk for disease [28] and the concept is also applied in epilepsy genetics to find the liable epileptic gene traits in the population study and the results has been shown to cross the liability threshold model, and the traits had variability within the population, influenced by both genetic and non-genetic factors [29]. Dozens of genes with de novo pathogenic variants have been identified and the number continues to grow in developmental and epileptic encephalopathy's (DEE) but the genetic etiology is more complex in case of GGEs and non-acquired focal epilepsy (NAFE).

Genomic hotspots are the regions that are under recurrent losses and gains of small genomic regions in the human genomic architecture [30]. Genetic risk factors predisposing to human epilepsies may vary in size, from a single base pair to greater than one million. Due to hotspot rearrangements many of the micro deletions has been identified in neurodevelopment disorders, including epilepsy.

Steward et al. (2019) studied on re-annotation of DEE associated genes and updated the GENCODE gene annotation for 191 epilepsy-associated genes, and created 3,550 putative transcript models using human brain transcriptomic libraries and other data sets. They screened 122 people with Dravet syndrome or a similar phenotype with a panel of exon sequences representing eight established genes and identified two de novo SCN1A, due to its close phenotype/genotype correlation with Dravet syndrome. The research identified potential gain of thorough gene annotation to improve diagnostic yields for genetic disorders [31].

During development of foetus about half of all genes are expressed in the brain and therefore they can be considered as candidate genes of seizure disorders [32]. In that order, a novel gene study on netrins in neurodevelopment disorders are being studied in different populations and their role and function in the neuronal network are yet to be fully establish. Netrins are the G protein receptor, vertebrate-specific synaptic cell adhesion molecules play the role in synapse structure and function and co-evolved to contribute in higher brain functions. Abnormal expression of Netrin-Gs has been associated with behavioural phenotypes in mice, and with possible involvement with schizophrenia, bipolar disease, TLE, and Rett syndrome (RTT) in humans [33].

Netrin-G2 gene on chromosome 9q34.13 is predominantly located in the pre-synaptic membrane, act as an excitatory neurons .During development of the central nervous system, netrin-g2 is expressed and where it may function as a local guidance cue for axonal growth and may influence synapse formation and neuron migration [34,35]. Pan et al. (2010) expression study on netrin-G2 protein in humans and mice showed abnormal expression of netrin-G2 protein in the pathophysiology of TLE and of netrin-G2 protein is over expressed in the temporal neocortex of patients with intractable epilepsy (IE). Netrin-G2 was also up regulated concurrently with the time from seizure induction in the TLE rat model. They also observed many fibrous nerve processes surrounding the immunoreactive cells in the brains of TLE rats and more immunoreactive neurons clustered in the cortex of both IE patients and epileptic rats compared to the controls. Under physiological conditions netrin-G2 is expressed and the expression is increased after seizures and abnormal formation of the neuronal network is an important factor leading to IE. Netrin-G2 may play a role in IE and affect neuron migration during IE development [36].

Abu-Libdeh et al (2019) study stated that NTNG2 as a candidate disease gene and identified a homozygous frame-shift variant in NTNG2 (NM_032536.3: c.376dup), encoding netrin-G2, in eight individuals from four families with global developmental delay, hypotonia, secondary microcephaly, and autistic features by an exome analysis and Sanger sequencing methods by comparing the data to knockout mice of*ntng2* [37].

When the neuron migration is not normal, obviously development of nervous system will be abnormal, this may be the background etiology of epilepsy [38, 39].An anatomical basis for the recurrent excitatory loop based on the abnormal synapse formation. Abnormal synapses spread the epileptic discharges and the excitatory loop will be formed due to the synapses reorganization [40].These changes in synapses leads to frequent seizures and promote the formation of IE. Recent studies have suggested that the growth of axons and neuron migration may be mediated by the same ligand-receptor mechanism [41]. In the future more research work need to be carried out on neurodevelopment candidate gene like netrins will make an evitable result in understanding the etiology of seizure in clear cut.

Research thrust for epilepsy molecular level expression studies travels in various paths, like finding the traditional medicine effects on epilepsy and their protective role to get application-oriented results by studying the signalling pathways are also in trend. *Bombyx batryticatus* has been utilized to treat convulsions, epilepsy, cough, asthma, headaches, and purpura in traditional Chinese medicine systems etc. [42-44]. Meibian Hu et al., (2019) investigated on *Bombyx batryticatus* (BBPs) derived protein-rich extracts and studied their antiepileptic effects on PTZ and MES -induced seizure in mice and exploring the protective effects of BBPs

against H2O2-induced oxidative stress in PC12 cells and their underlying mechanisms. Results of the investigation revealed that the BBPs showed high potential antiepileptic effect in seizure induced mice models and possessed high anti-oxidative and anti-apoptotic effects in PC12 cells via PI3K/AKT signalling pathway. Study showed BBPs up regulated the expressions of PI3K, Akt, p-Akt, and Bcl-2, whereas down regulation was observed in the expressions of caspase-9, caspase-3, and Bax in H2O2-induced oxidative damage in PC12 cells [45].

Glucose is the soul energy of our brain metabolism. Transportation of glucose across the blood brain barrier occurs through glucose transporter (GLUT1) to the brain. SLC2A1 gene codes for the GLUT1, when mutation in the gene SLC2A1 results in low level of glucose and low level of lactate in cerebrospinal fluid. About 10% early onset childhood absence epilepsy was observed due to mutation in SLC2A1gene. Low glucose levels of CNS associated with many forms of GGE including JME, AE, generalised tonic-clonic seizures and condition associated with them includes ataxia, dystonia, choreoathetosis (movement disorder) and tremor were seen [46-49]. By means of genetic diagnosis, individuals can be treated and get benefitted by therapeutic implication of Ketogenic diet [50]. Early onset infantile epileptic encephalopathy (EIEE) are group of disorders characterised by an early onset and typically refractory to treat seizure with high mortality [51].Global developmental delay, movement disorders, autism and behavioural issues are associated with EIEE [52]. Timely and accurate diagnosis of EIEE in neonates can be achieved using molecular diagnosis e.g., GLUT1 deficiency or vitamin B6 dependent early onset epilepsy in new-borns can provide treatment options [53,54].

Ionic homeostasis is maintained by certain proteins in the brain. When there is a mutation in genes expressing this protein found to be a cause for seizure or epilepsy. An activity dependent ion concentration shifts results in ictogenesis. Na+-K-+ATPase to maintain cation get altered when chemically induced and tetanic stimulation of afferents resulting in seizure activity due to increase in K_0+ efflux and large Ca2+ influx. Altering both neurotransmitter release probability and magnitude of Ca2+ dependent K+ conductance [55].

ARX or aristaless related homeobox gene, a transcription factor, is an important determinant of neuronal migration and their mutation results in failure of interneuron migration to cortical target [56]. This unsuccessful migration collapse the neuronal network and connectivity in neuronal circuit and engendering epileptic circuitry due to abnormal differentiation or incomplete migration of interneuron [57,58] and are associated with EEs[59].

Glutamate interacts with N-Methyl-D-aspartate receptor subunits (GRIN2A, GRIN2B.GRIN1) found to have implication in FE [60-62]. Among this GRIN2A gene is mostly studied in epilepsy-aphasia and Rolandic epilepsy phenotypes, and in severe infantile-onset epilepsy[63-66].Hot water epilepsy caused by SLC1A1 genetic variants[67] and SLC1A2 is a glutamate transporter gene mutation found to be involved in epileptic encephalopathy and in focal seizures[68].COL4A1 andCOL4A2 are the genes coding for the collagen alpha subunits. Genetic alteration in these genes are found to involved in brain malformation due to pathogenic vascular events, cerebral haemorrhage and resulting in focal epilepsy[69-71].

Non-ion channel genes have minor role in the etiology of idiopathic epilepsies. LGI1 gene (leucine-rich glioma inactivated gene 1) have been shown to be a cause of an autosomal dominant partial epilepsy with auditory features (AD-PEAF). LGI1 gene codes for a protein characterized by a leucine-rich repeat motif (LRR) in its N-terminal end and in the C-terminal half epilepsy-associated repeats (EARs) [72, 73].Chabrol *et al.*(2007) identified 2 respective mutations in a French and an Algerian family with ADLTE [74]. Morante-Redolat *et al.* (2002) identified 2 truncating mutations in Spanish ADLTE families by direct sequencing [75].

Myoclonic epilepsy and ragged-red fibre disease (MERRF) is characterized by myoclonus, generalized epileptic seizures, myopathy, and slowly progressive dementia. MERRF occurs in individuals inheriting a different mixture of normal and mutated mitochondria from mother and most commonly found MERRF mutation is mt8344A>G that affects the tRNA Lysine gene within the mtDNA. Major mutations in the mitochondrial DNA are located in either one of three t-RNA genes, t-RNA$^{\text{Leu (UUR)}}$, t-RNA$^{\text{LYS}}$, or t-RNA$^{\text{Ile}}$, and

impairment in t-RNA maturation resulting various neuromuscular and neurodegenerative disorders[76].

Aquaporin 4 (AQP4) is widely found in the central nervous system (CNS), especially in astrocytes regulate water homeostasis and maintain potassium ion concentration (Kir4.1 is to carry potassium ions into cells accompanied by water entry through AQP4) reduce the excitability of neurons [77,78]. AQP4 was found to be significantly increased in protein levels in surgical resection from patients with refractory temporal lobe epilepsy (TLE) and may be involved in epileptic drug resistance [79]. Studying relevant brain structures (e.g. Hippocampus) of ante-mortem brain tissues after epilepsy surgery provide opportunities for gene expression [80] and allow us to directly investigate on transcriptional programmes in brain tissue. SESN3 might regulate neuroinflammatory molecules, previously implicated in epilepsy [81-84] through modulation of oxidative stress in the brain. Using genome-wide Bayesian expression QTL mapping [85], found Sestrin3 (*SESN3*) as a trans-acting genetic regulator of the pro-convulsant gene network in the human epileptic hippocampus. Independent experimental studies in vitro and in vivo systems, validated the genetic regulation of the pro-convulsant transcriptional programme in epilepsy by Sestrin 3, therefore providing a first evidence of a function for SESN3 in disorders of the human brain for the first time revealed SESN3-dependent regulation of epileptogenic IL-1b3 and TLR-signalling genes and in zebra fish are SESN3 play the role in regulating proinflammatory cytokines and their downstream effect on CNS excitability and seizure susceptibility [86]. Female specific epileptic genes (Table 2) mutation occurs in GABRA1,STXBP1 and PCDH19[87-89].The advances in the mTOR pathway provide potential therapeutic strategies and mTOR pathway mutations is an important area of current research [90] and direct inhibitor targets of mTOR regulators therapeutic values in epilepsy genetic era and specificity of targets will be crystal clear for treatment [91]. Germ line mutation associated with FE and with or without brain malformation was observed and studied in the following genes AKT3, DEPDC5, MTOR, NPRL2, NPRL3, PIK3CA and PIK3R2[92-100].Somatic cell mutation of post-mortem brain tissue study included AKT3, DEPDC5, MTOR, PIK3CA, TSC1, and TSC2 [92,,101-103].

Conclusion

Recent methodologies like NGS, WGS, WES, transcriptomic gene profiling, and study of epilepsy genes in optogenetics, polymorphism study of SNP in individual vs population study, bioenergetic mechanism focusing of mitochondrial DNA and mTORpathway research and genes of developmental neurobiology (netrins and ARX) involved in epileptic mechanism yet to be studied in detail. As of now 400 genes are commercially available for panel testing of genes for clinically heterogeneous individuals [104]. AQP4,SESN3,ARX,NTNG1 and NTNG2 genes and TSC1 and TSC2 are the genes need more attention of the researchers involved in epilepsy genetic studies. One more gene named CLN or NCL with many subtypes involved in different pathological condition of epilepsy and in ceroid neuronal lipofuscinoses belongs to lysosomal storage disease is an inherited autosomal neurodegenerative disorder[105].As there are many different subtypes an exact underlying mechanism yet to be elucidated in detail [106].

Comments

Novelty is a good quality of research and novel genes of epilepsy yet to make clear statements may provide quality research ideas and application of advanced methods and advance technologies to the researchers.

Appendix

Abbreviations refer APPENDIX I

Acknowledgment

None

Epilepsy

Genetic generalized epilepsy (GGE) Focal epilepsy (FE) Epileptic encephalopathy (EE)

Figure: 1 Schematic representation for classification of epilepsy.

Table 1 Types of waves recorded in EEG

Rhythm	Frequency(waves/sec)	Activity	Remarks
Delta	up to 4	slowest type of wave but have the highest amplitude (strongest signal)	Common in children under 1year.Association of seizure-like activity found within the brain. W. Grey Walter used delta waves from an EEG to locate brain tumors and lesions causing temporal lobe epilepsy.[5]
Theta	4-7	slow activity	Occur during sleep and in young children. not obvious in adults who are awake.
Alpha	8-13	Larger amplitude slower frequency	Typical for adults whose eyes are closed and relaxed. Clearest in the occipital lobes.
Beta	12.5 – 30	Smaller amplitude faster frequency	multiple and varying frequencies are often associated with active, busy or anxious thinking and active concentration.
Gamma	32-100		During a focal seizure event, maximal gamma rhythm synchrony of interneurons is always observed in the seizure onset zone, and synchrony propagates from the onset zone over the whole epileptogenic zone.[6]

Table 2 Epileptic genes of female specificity

Gene name	Abbreviation	Gene function	Molecular
Gamma-Amino Butyricacid Receptor,Alpha1	GABRA1	Effect on inhibitory control of neuronal circuits	denovo he
Syntaxin-Binding Protein1	STXBP1	synaptic transmission and immunoactivity	denovo he
Protocadherin19	PCDH19	Cognitive function	Protein te

APPENDIX I.

Abbreviations:

Ach : Acetylcholine

AD- PEAF: autosomal dominant partial epilepsy with auditory features.

ADLTE : autosomal dominant lateral temporal epilepsy

ADNFLE : autosomal dominant nocturnal frontal lobe epilepsy.

AKT3 : AKT serine/threonine kinase 3.

AQP4 : Aquaporin 4

ARX : aristaless related homeobox X-linked gene

BBPs : *Bombyx batryticatus* ()

CAE : Childhood absence epilepsy.

CHRNA4 : Cholinergic receptor, neuronal nicotinic, alpha polypeptide.

CNS : Central nervous system.

COL4A1 : Collagen type IV alpha 1 chain

COL4A2 : Collagen type IV alpha 2 chain

DEE : Developmental and epileptic encephalopathy's

DEPDC5 : DEP domain containing protein 5.

EARs : Epilepsy-associated repeats.

EE : Epileptic encephalopathy

EEG : Electroencephalogram

EIEE : Early onset infantile epileptic encephalopathy ()

FE : Focal epilepsy

GABA : Gamma amino butyric acid.

GGE : Genetic generalized epilepsy

GLUT1 : Glucose transporter 1

GRIN : Glutamate receptor ionotropic N-Methyl-D-aspartate receptor subunits.

ID : Intellectual disability.

JME : Juvenile myoclonic epilepsy.

KCND3 : Potassium voltage gated channel, SHAL related subfamily member 3.

KCNJ10 : Potassium channel, inwardly rectifying, sub family J, member 10.

Kir : Killer cell immunoglobulin like receptor

LGI1 : Leucine-rich glioma inactivated gene 1.

LRR : Leucine-rich repeat.

MERRF : Myoclonic epilepsy and ragged-red fibre disease

MTOR : Mechanistic target of Rapamycin.

mV : millivolt

NAFE : Non-acquired focal epilepsy.

NPRL2 : NPR2 like protein.

NTNG1&2: Netrin-G1 and G2

PCDH19 : Protocadherin 19

PIK3 : Phosphotidyl inositol 3-kinase

PWE : Patients with epilepsy.

RTT : Rett syndrome

SESN3 : Sestrin3

SNV : Single nucleotide variant.

STXBP1: Syntaxin binding protein 1

TLE : Temporal lobe epilepsy.

TSC1 &2: Tubersclerosis subunit 1 and 2

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Correspondence Author – Poornima Kannappan, Department of Biochemistry, Karpagam Academy of Higher Education, poorniovya@gmail.com, biochemmeenakshi@gmail.com, +91-9629525228.