Azhar Int J Pharm Med Sci 2025; Vol 5 (1): 27- 37
(Review Article)

Open Acces

Print ISSN: 2735-4598
Online ISSN: 2735-4601

Gene polymorphism in epilepsy_ review article

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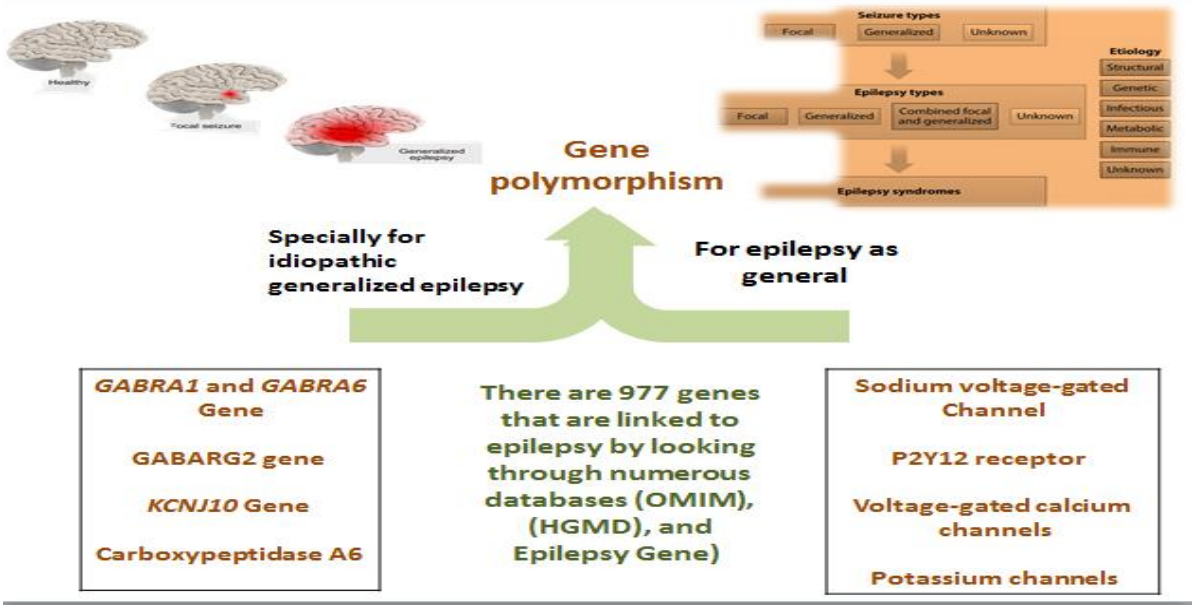
Article history: Received 2023-12-17 **Revised 2024-05-27** **Accepted 2024-07-12**

Abstract: More than 50 million people globally experience epilepsy, a spectrum of diverse brain illnesses wherein recurrent epileptic seizures are the hallmark. According to International League Against Epilepsy (ILAE) four basic forms of epilepsy are distinguished: focal, generalized, combination generalized and focal, and unknown. Epilepsy may have obvious structural, infectious, metabolic, and immunological etiologies, and its etiology appears to be mostly influenced by genetics, but in the majority of cases, no obvious etiology is found. Early connected studies have identified numerous loci which might include possible genes linked to epilepsy susceptibility, and mutational research have discovered a number of mutations in both ion channel and non-ion channel genes in idiopathic generalized epileptic patients. Such genes may generally cause epilepsy, or they may account only for different types of it. In this article we demonstrated some of these genes and its direct correlation with epilepsy and the specific type idiopathic generalized epilepsy.



Keywords: Epilepsy; Idiopathic epilepsy; Epilepsy genes; Gene polymorphism, Ion channel.

1. INTRODUCTION

Epilepsy is a brain illness distinguished by a persistent propensity to cause seizures as well as neurobiological, psychological, cognitive, and social implications[1].

A major public health concern, epilepsy is characterized by aberrant neural discharges or through synchronized neurons' hyperexcitability. Epilepsy is a multifactorial neuronal disorder[2]. Recurrent seizures are a hallmark of epilepsy, which

has one of the highest rates of occurrence among illnesses of the central nervous system (CNS). Patients with uncontrolled epileptic seizures have a lower quality of life because they raise their risk of bodily harm, impairing their physical health, and impairing their psychosocial functioning [3].

1.1. Prevalence of epilepsy

Epilepsy affects around 50 million individuals globally, with 80% residing in low- and middle-income nations [4].

Epilepsy is one of the most common neurological diseases, with a point prevalence of 4 to 10 per 1,000 people, according to previous studies. It is estimated that there are 50–60 cases of epilepsy for every 100,000 person-years. Epilepsy affects people of all ages and genders worldwide. Men are slightly more likely than women to have epilepsy, both in prevalence and incidence [5].

There are insufficient epidemiologic data on epilepsy in Egypt. Epilepsy has a comparatively high incidence and prevalence in Upper Egypt [6].

1.2. Pathophysiology of epilepsy

A fundamental biological process called epileptogenesis causes spontaneous seizures in response to brain injury as well as the first recurring epileptiform event. It deals with the patient's epilepsy's onset and progression. The biological processes, structural, and functional changes are involved in epileptogenesis. The epileptic mechanism involves a number of neurotransmitters, several of which are crucial. Serotonin, gamma-aminobutyric acid (GABA), glutamate, dopamine, and noradrenaline are the most significant neurotransmitters. GABA and glutamate are the two neurotransmitters most frequently researched in relation to epilepsy. Variations in GABA-mediated inhibition and glutamate-mediated excitement contribute to neuronal hyperexcitability in epilepsy. Neurons that have been depolarized by glutamate produce excitatory post-synaptic potentials [7].

Particular glutamatergic molecular pathways, including an increase in the amount of glutamate in extracellular space, increased glutamate receptor expression, and specific anomalies in glutamate transporters, take place during the onset and course of epilepsy. Due of increased glutamatergic activity, these processes lead to neuronal hyperexcitability. One of the main inhibitory neurotransmitters is GABA. Pre-synaptic potentials are produced by hyperpolarizing the neurons. It is essential for both balancing neuronal excitement and preventing epileptiform discharges. The epileptogenesis involves the GABAA and GABAB receptors [7]. Loss of GABAergic processes can raise a person's risk of developing epilepsy [8].

1.3. Etiology of epilepsy

Six kinds of etiologies were suggested by Position paper on epilepsies classification by (ILAE): structural, infectious, genetic, immunological, metabolic, and unknown. Based on all information known up to the age of seven and genetic discoveries at any age, the etiology was determined [9] (Figure 1).

According to the majority of research, 40 out of every 100 instances of epilepsy have a known etiology,[1]and more than 50% of people who suffer from epilepsy do not know what causes their seizures. In the 1989 seizure classification, certain kinds of epilepsies were labeled as "idiopathic"[10].

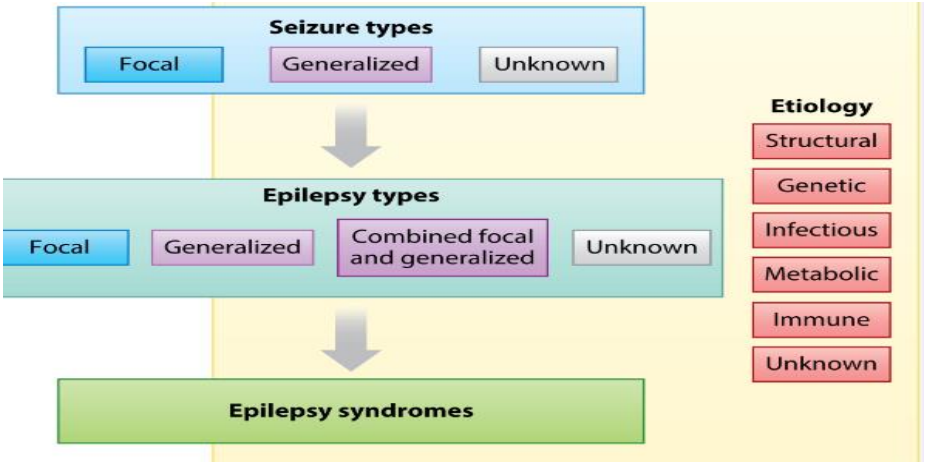


Figure 1. Etiology of epilepsy [9].

2. HOW TO DIAGNOSE EPILEPSY

The term "epileptogenic zone" designates a section of the brain that experiences aberrant electrical activity, or "epileptic seizures." The epileptogenic zone mostly determines the epilepsy symptoms. Making a diagnosis and initiating the suitable antiepileptic medication is important since it identifies whether the seizure is focal or generalized. Knowing the site of the epileptic fit is crucial for developing effective management options, particularly for surgical therapy [11].

2.1. Magnetoencephalography (MEG)

When a patient is being evaluated for epilepsy surgery, a neurophysiologic test called magnetoencephalography (MEG) allows for the functional localization of epileptic etiology. MEG is a non-invasive method that monitors brain activity as it is reflected outside the skull as electrical currents create magnetic fields in neurons. MEG has heightened tangential sensitivity inputs from cortical planes and sulci than EEG [12].

2.2. Electro-encephalogram (EEG)

The electrical activity of the brain, or the dynamics of the brainwaves, is measured by EEG. During an EEG, 19 electrodes are typically utilized (along with system reference and ground) to detect and record the electrical discharge events in the brain. EEG can both clarify the type of epilepsy and confirm a diagnosis [13].

Epilepsy is diagnosed mainly on clinical data, and it is best to consider the EEG as confirming rather than diagnosing. The adage "handle the patient rather than the EEG" is the norm [14].

2.3. Magnetic resonance imaging (MRI)

In addition to the clinical assessment and the EEG, MRI scans are crucial in evaluating a person with seizures. When a patient has focused seizures, unusual neurologic symptoms, or focal EEG discharges, MRI is more likely to reveal an anomaly. MRI is favored over computed tomography (CT) because it is more sensitive, especially when looking for cortical malformations, hippocampal sclerosis, or developmental abnormalities. There are a number of new imaging techniques that can help in epilepsy assessment [15].

If the patient has epileptiform activity on their EEG or detects aberrant epileptogenic brain imaging, they may experience recurring seizures[16].

2.4. Neuropsychological tests

To assess thinking, memory, speech skills to determine which brain regions are impacted. Throughout the previous 25 years, there has been a notable change in the neuropsychological assessments importance in the care of epileptic patients[17].

3. CO-MORBIDITIES AND EPILEPSY

Co-morbidities that are frequently associated with epilepsy include cognitive dysfunction, which includes issues with processing, memory, and attention, mental health issues, such as anxiety or depression, and somatic co-morbidities, such as migraines and sleep problems. Comorbidities with epilepsy are frequent and frequently harsh. The co-morbidities are often more difficult for people with epilepsy than the seizures [18].

Epilepsy sufferers have a high risk of cognitive impairment, which hinders their ability to succeed in school and in life. There is a recognized difference between IQ and achievement in half of children with epilepsy, and low IQs are more common. Regression in cognitive ability can also occur in adults with epilepsy. People who experience frequent recurrent seizures, status epilepticus (SE), or extended seizures lasting 30 minutes or more are especially vulnerable to brain damage that can cause cognitive deficits [18].

3.1. Mortality outcomes

It is widely acknowledged that individuals with epilepsy are more likely to die young (by a factor of 2 to 3 compared to the general population). Suffocation, aspiration of stomach contents, among the several causes of mortality for children and adults with epilepsy are a brain tumor, brain damage, drowning, SE, sudden unexpected death in epilepsy (SUDEP), accidents, and vascular illness [19].

4. TREATMENT

The goal of treatment for epileptic patients is to stop seizures without having any unfavorable side effects. More than 60% of people who need antiepileptic drugs (AEDs) have achieved this aim. However, a lot of patients have unpleasant adverse effects with these medications, and some patients experience seizures that do not improve with conventional medical treatment. Less than two thirds of individuals with newly diagnosed epilepsy are seizure-free after a year, according to a 2017 study. According to the more recent research, 64% of participants did not experience seizures [20].

AEDs have developed new modes of action in recent years, making the management of epilepsy a difficult task [21, 22].

5. EPILEPSY CLASSIFICATION

ILAE, founded in 2017, has the most recent epilepsy classification. Epilepsy is categorized

using a variety of criteria, such as mode, seizure type, family history, age of onset, EEG, and MRI results [23].

Four primary types of epilepsy are distinguished: focal, generalized, combination generalized and focal, and unknown [24] (Figure 2).

When abnormal electrical activity starts in one brain hemisphere and spreads to the other, it is known as a focal seizure.

A focal to a bilateral tonic-clonic seizure is when only one or both limbs jerk; this can happen. A generalized seizure, however, causes aberrant electrical activities to occur simultaneously from both cerebral hemispheres [25].

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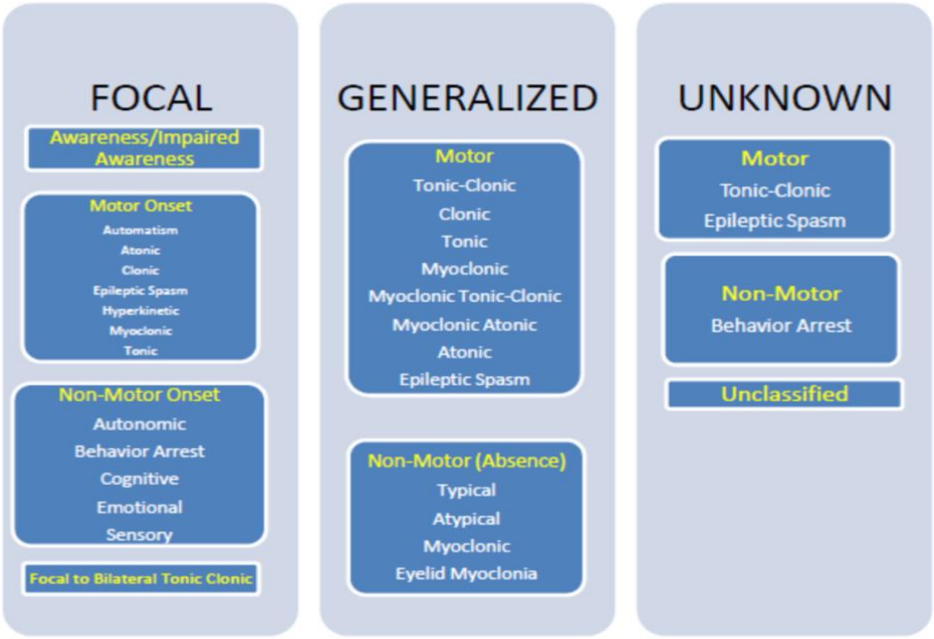

Figure 2. ILAE 2017 Classification of Seizure Types: Expanded version [24].

6. GENE POLYMORPHISM IN EPILEPSY

A growing number of genes linked to epilepsy have been found because of advancements in genetic research. We discovered 977 genes that are linked to epilepsy by looking through numerous databases (the Human Gene Mutation Database (HGMD), the Online Mendelian Inheritance in Man database (OMIM), and Epilepsy Gene) and current articles on PubMed [26].

We listed below some of the most common genes that affect pathogenesis of epilepsy.

6.1. Polymorphisms of sodium voltage-gated channel genes.

The proteins known as sodium voltage-gated channels (*SCNs*), which contain either alpha or beta subunits and are present in endocrine and neurological cells, play essential roles in the action potential generation. The sodium ion influx that is necessary for neurons to start an action potential is mediated by the *SCN*. As a result, *SCN* gene alterations may affect the onset and progression of epilepsy [27].

SCN1A is found on chromosome 2, have 26 exons and cover more than 100 kb of genomic DNA. This gene has been linked to Familial Febrile Seizures (FFS) and Genetic Epilepsy with Febrile Seizures Plus (GEFS+). GEFS + is a type of epilepsy that is found in families, whereas FFS is prevalent in children who are six months to five years old.[28]Additionally, *SCN1A* was connected to dravet syndrome (DS), a severe epileptic encephalopathy that is inherited and increases the risk of abrupt, unexpected death in epileptics [28].

SCN2A mutations have recently been linked to the disease known as infantile epilepsy with migratory focal seizures (EIMFS) [29].

SCN1B and *SCN2B* have been linked to dravet syndrome [30].

In another study according to (Alghamdi et al., 2022) who discovered that the *SCN1A* gene's rs6432861 allele was correlated with the probability of epilepsy ($p = 0.014$). Additionally, the *SCN2A* gene's rs4667485 and rs1469649 substantially linked

with the likelihood of developing epilepsy. Additionally, the examination of haplotypes showed that the *SCN2A* gene's GATGCTCGGTTTCGCTACGCA haplotype was substantially associated with an elevated risk of epilepsy. According to our findings, many of the *SCN* variations that were under investigation in the present study were connected to a number of epilepsy-related clinical characteristics [27].

6.2. Apolipoprotein E

The human Apolipoprotein E (*APOE*) gene, that codes for a protein with 299 amino acids (about 36 kDa), is found on chromosome 19 at location q13.32. The three primary sections of *APOE* are a C terminal section with the lipid-binding site and three helices, a N terminal area with the receptor-binding site and four helices, and an intervening flexible hinge area that joins the N- and C-terminal areas [31].

APOE is a glycoprotein that is primarily made by astrocytes and hepatocytes and is present in plasma and cerebrospinal fluid. It contributes to the metabolism of fats and cholesterol homeostasis [32].

The *APOE* locus contains three main alleles, ε2, ε3, and ε4. The combination of variations at 2 single nucleotide polymorphisms (rs429358 and rs7412) defines the three main alleles (2, 3, and 4). The two most frequent SNPs are rs429358 (C > T) and rs7412 (C > T), which cause changes in the amino acids at positions 112 and 158 of the *APOE* protein, respectively [33].

Numerous investigations have demonstrated that the *APOE* ε4 allele can cause increased cortical excitability, decrease GABA interneuron density, and impairment in brain function[34]. Gamma oscillations may decrease if this neuron's activity is inhibited [35]. Because of the decrease of GABAergic interneuron activity, *APOE* ε4 carriers have an excitable network [34].

As per current evaluations, there is an increase in the pro-inflammatory response due to APOE ε4, which further results in BBB malfunction and cognitive impairments [36].

6.3. *P2Y12* receptor gene polymorphisms

A member of the metabotropic (P2Y) receptor family is the *P2Y12* receptor., is exclusively expressed in the CNS's microglia[37]and is crucial for maintaining synaptic plasticity and brain homeostasis,[38]vascular healing[39], as well as microglia's chemotaxis and motility[40]. According to preliminary studies, microglial *P2Y12* receptors (*P2Y12Rs*) have a part in the epilepsy pathogenesis by controlling relationships between neurons in the brain, abnormal neurogenesis, or immature projections from neurons. The findings suggested that individuals carrying the G allele of rs1491974 G>A or rs6798347 G>A might have a higher chance of developing epilepsy[41].This is most likely because, during the seizure-onset phase, the ATP generated by hyperactive neurons promotes neurons-microglia interaction via *P2Y12R* and, as a result, suppresses neuronal activity via A1 receptors[42]. Subsequent research revealed that the development of epilepsy was facilitated by a *P2Y12R*-dependent mechanism in microglia that enhanced immature neural projections and encouraged aberrant neurogenesis after seizures[43].

6.4. Voltage-gated calcium channels

The voltage-gated calcium channels (*VGCCs*) in the mammalian (CNS), control intracellular signaling and gene regulation as well as the inflow of calcium ions in reaction to the depolarization of membranes. Ten genes code for the subunits, which are the calcium channel's main pore-forming subunits. These subunits have 6 transmembrane domains apiece and 4 homologous domains (DI-DIV), with the inner pore of the channel being lined by the S5 and S6 transmembrane segments. Numerous human illnesses, including epilepsy, are linked to these genes, many of which have expression patterns that are unique to cells and tissues[44]. In a recent investigation, Helbig et al. identified 30 people with developmental and epileptic encephalopathy (DEE) due to de novo gain-of-function missense mutations in *CACNA1E*. A class of severe epilepsies known as DEE cause developmental delay and refractory seizures [44].

Because calcium has a divalent positive charge, it quickly enters neurons and depolarizes the cell membrane potential, which in turn regulates biophysical processes such as oscillations of membrane potential and action potential firing. The regulation of the molecular apparatus and intracellular signaling channels required for physiological functions, such as the release of neurotransmitters is the second effect of calcium ion influx, so small changes in their biophysical characteristics or expression might cause pathological modifications in the brain that may lead to epileptic episodes [45].

6.3. Potassium channels

This is the most complex and diverse ion channels`family. Potassium channels are essential for numerous biological processes and have a noteworthy effect on both the pathophysiology of epilepsy and the outcomes of targeted therapy.[46]K+ may flow quickly and selectively through the electrochemical gradient across the cell membrane through potassium ion channels based on their

physiology, pharmacological sensitivity, biophysical characteristics, and structure[47].

A significant fraction of ion channel-related epilepsy is caused by mutations in the potassium ion channel gene. As next-generation sequencing technology advances, more patients' pathogenic genes causing genetic epilepsy are being found. We discovered that potassium channel gene mutations represent a significant part of instances through numerous large-scale genetic testing studies in China, showing that potassium channel genes play a crucial role in the genesis of epilepsy[48.] Potassium (K) channels have a variety of relationships with epileptic disorders, from direct regulation of neuronal excitability and ion milieu balance to indirect effects through metabolism [49].

After we talked about these previous genes, we are going to choose a specific type of epilepsy to illustrate its correlation with some genes.

7. GENE POLYMORPHISM IN GENERALIZED EPILEPSY

Idiopathic generalized epilepsy, is a type of epilepsy which do not, by definition, have structural abnormalities of the brain visible on MRI, in addition to having no symptoms or external signs, ruling out the majority of the etiological categories [50].

Idiopathic epilepsy is strongly correlated with genetic variables.[6]This prompted ILAE to adopt the term "genetic generalized epilepsies" in place of the phrase "idiopathic epilepsies"[8].

There are more than 20 genes that are known to be highly susceptible to "idiopathic" epilepsies. [8]Idiopathic epilepsy syndromes are significantly influenced by genetic factors. The pathophysiology of idiopathic epilepsies is influenced by ion channel genes as well as some non-ion channel genes [51].

7.1. *GABRA1* and *GABRA6* gene mutations

The inhibitory neurotransmitter gamma-aminobutyric acid (GABA) operates on particular postsynaptic membrane GABA receptors to promote hyperpolarization by making the conductance of chloride higher and thereby preventing further action potential production [52] (Figure 3).

The GABA receptor genes *GABRA1* and *GABRA6* are particularly prone to IGE-linked mutations, some of which are harmful and have been thoroughly investigated. Over 30 *GABRA1* mutations have been associated with different forms of epilepsy as of this writing [53].

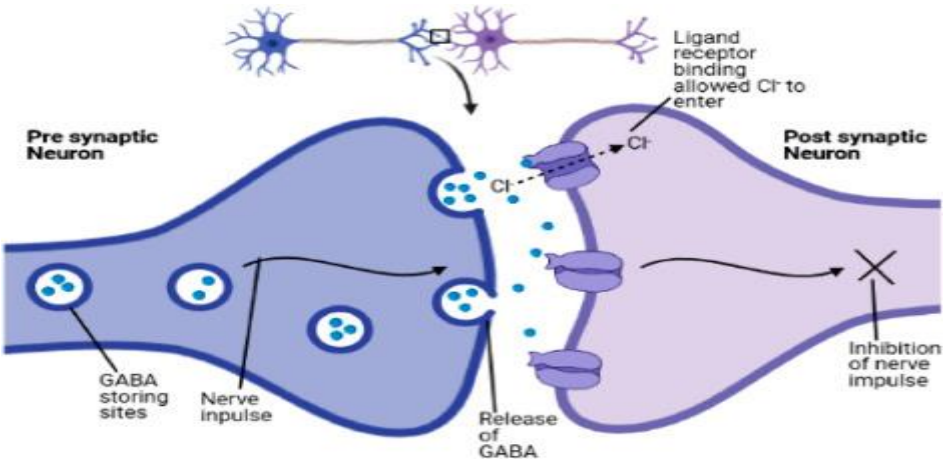

Figure 3. Inhibitory role of GABA [53].

These variations have been shown to alter the receptors' composition, trafficking, expression, and ion channel gating, lowering GABAergic inhibition and causing epileptogenesis.[52] Studies conducted in vitro reveal that a considerable number of *GABAA* receptors with altered α1 subunits frequently display decreased GABA sensitivity and smaller current amplitudes. This may indicate a reduction in inhibitory activity and, consequently, a higher risk of seizures occurring in vivo [54].

Of the five mutational sites examined, two *GABRA1* (rs2279020 and new c.1016_1017insT) and two *GABRA6* (rs3219151 and novel c.1344C>G) mutational sites were shown to be significantly correlated with IGE. In *GABRA1*, a novel insertion mutation called c.1016_1017insT disrupted the reading frame and might have resulted in harm, while in *GABRA6*, c.1344C>G generated a synonymous mutation, according on amino acid alignment. Therefore, it is possible that both *GABA*

receptor genes are crucial in the emergence in Pakistani epileptic patients[55].

7.2. "C588T" of *GABARG2*

The *GABARG2* C588 T polymorphism may affect how patients respond to antiepileptic medications and is linked to a higher chance of developing IGE in children [56].

The findings revealed that *GABRG2* may be a possible treatment goal for epilepsy and that the *GABRG2* C588T polymorphism may affect the *GABAA* receptor through regulating *GABRG2* gene expression, causing epilepsy risk [57].

7.3. Gene Polymorphisms in *KCNJ10* for Childhood Epilepsy

Numerous genes that have been found encoding voltage-gated or ligand-gated ion channels. Maintaining potassium balance, connecting membrane excitability with the metabolic status of the cell, and controlling resting membrane potential all depend on the inward-rectifying potassium channel (Kir). The Kir4.1 channel, an inwardly rectifying potassium (K+) channel, is encoded by the gene potassium inwardly rectifying channel subfamily J member 10 (*KCNJ10).* When these channels are genetically inactivated in glia, extracellular K+ and glutamate clearance are compromised, leading to a seizure-related phenotype. Polymorphisms and mutations in the *KCNJ10* gene have been connected to mice's and humans' susceptibility to seizures [58].

Individuals with idiopathic generalized epilepsy (P =.037) and generalized tonic-clonic seizures (P =.0015) showed statistically significant relationships with the G/T genotype of the *KCNJ10* gene. Patients who experienced generalized tonic-clonic seizures also had higher T allele levels (P =.0158). Nevertheless, a statistically significant association between epilepsy and the rs61822012 polymorphism was not found. Our results imply that the rs2486253 polymorphism of the *KCNJ10* gene, which is associated with the G/T genotype, affects the likelihood of common kinds of infantile epilepsy. For tonic-clonic epilepsy, the T allele of this polymorphism has been identified as a seizure-susceptibility allele [58].

7.4. Carboxypeptidase A6 (*CPA6*)

The enzyme *CPA6* belongs to the M14 metallocarboxypeptidase family, which was found in 2002 during an investigation for new metallocarboxypeptidase genes. It is a 50 kDa proenzyme with a prodomain that helps the enzyme fold and keeps it from activating inside the cell. When CPA6 adheres to the extracellular matrix (ECM), it becomes active enzymatically, and is released as a 37 kDa mature enzyme without the prodomain. *CPA6*, like the other enzymes in this subfamily, cleaves the C-terminal amino acids from peptides and proteins. C-terminal proteolytic cleavages are significant post-translational modifications that have the ability to change, destroy, or activate signaling molecules. We screened individuals with juvenile myoclonic epilepsy for mutations in the *CPA6* gene and discovered two novel missense mutations: Arg36His and Asn271Ser. In addition to these mutations, patients had generalized epilepsy when they were first diagnosed. In a control population, neither of the unique mutations was discovered. In *CPA6* and additional relevant metallocarboxypeptidases, Asn271 is highly conserved. The prodomain contains Arg36, lacks a lot of conservation[59]. Studies suggested that a number of *CPA6* gene variants might affect carboxypeptidase activity, structural integrity, or both, and might thus be connected to the epilepsy [60].

8. Egyptian polymorphism in epileptic patients

Among the above-mentioned genes, there are (*SCN1A and GABRG2*), that have a polymorphism in Egyptian epileptic patients as follows:

The findings supported the hypothesis that the SCN1A c.3184 A/G polymorphism contributes to epilepsy and, in addition, to the pharmacoresistance in Egyptian children with epilepsy[61].

According to the current research, the GABRG2 (SNP211037)-C allele may be a useful genetic marker for predicting an Egyptian child's vulnerability to simple FS [62].

9. CONCLUSIONS

Since epilepsy is primarily a problem of neuronal excitability, its cause remains unknown. Epilepsy is divided into categories, and idiopathic generalized epilepsy is more common. Numerous gene mutations involving voltage-gated sodium channels (*SCN1A*, *SCN1B*, *SCN2A*, and *SCN2B*), potassium channels, calcium channels (*CACNA1A, CACNA1D*, *CACNA1G*, and *CACNA1E*), ligand-gated GABARs (*GABRA1, GABRA6, and GABARG2*), and many other genes that have linked to epilepsy as general or idiopathic generalized epilepsy specially have been discovered through genetic investigations. This article discussed only little few of the genes that commonly associated with epilepsy, and still there are many of them for further studies. We chose these genes to cover a wide range of genes that are linked to epilepsy differently, for example (*SCN1A*,

SCN1B, *SCN2A*, *GABRA*, *GABARG*, Potassium channels , *and CACNA1A*), mutations in these genes cause pure or relatively pure epilepsies, or syndromes with epilepsy as the core symptom. Another genes such as (*SCN1A*, *SCN1B*, *SCN2B*, *APOE4*, and *CACNA1E*), cause developmental delay and affect cognition together with epilepsy, while for (*GABRA1*, *GABRA6*, *GABARG2*, *KCNJ10*, and *CPA6*), they are related to idiopathic generalized epilepsy.

Funding: This article did not receive a specific grant from any funding agency in the public, commercial or not for specific sectors.

Acknowledgments: In this section you can acknowledge any support given which is not covered by the author contribution or funding sections. This may include administrative and technical support, or donations in kind (e.g., materials used for experiments).

Conflicts of Interest: The authors declare that they have no competing interest.

Ethical Statement: Interventionary studies involving animals or humans, and other studies require ethical approval must list the authority that provided approval and the corresponding ethical approval code.

Author Contribution: This work was carried out in collaboration between all authors.

List of Abbreviations: AEDs: Antiepileptic drugs; APOE: Apolipoprotein E; Arg: Arginine; CNS: Central nervous system; CPA6: Carboxypeptidase A6; DEE: Developmental and epileptic encephalopathy; DS: Dravet syndrome; EEG : Electro-encephalogram; FFS: Familial Febrile Seizures; GABA: γ-aminobutyric acid; GABAA: γ-aminobutyric acid A; GABAB: γ-aminobutyric acid B; GABRA1: γ-aminobutyric acid receptor A; GABRA6: γ-aminobutyric acid receptor A6; GABARG2: γ amma-aminobutyric acid type A receptor subunit gamma2; GEFS +: Genetic Epilepsy with Febrile Seizures Plus; HGMD: Human Gene Mutation Database; IGE: Idiopathic generalized epilepsies; ILAE: International League Against Epilepsy; IQs: Intelligence quotient; KCNJ10: Potassium inwardly rectifying channel subfamily J member 10; KDa: Kilodaltons; MEG: Magnetoencephalography; MRI: Magnetic resonance imaging; OMIM: Online Mendelian Inheritance in Man database; SE; Status epilepticus; SCNs: Sodium voltage-gated channels; SNPs: Single nucleotide polymorphisms; VGCCs: Voltage-gated calcium channels

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