Genetics of Epilepsy

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Abstract

Genetics is a branch of the human biology that provides insights into basic and vital processes which arise from birth till death, development to apoptosis (cell death), and in disease aetiology and therapies, or better methods in use of available treatments to solve human health conditions because genes function in all biological processes.

Epilepsy is a seizure that occurs without identifiable justification with a great chance of further seizures which is almost the same to the global recurrence risk of 60% after two unjustified seizures, happening over a ten years' span. Fifty million people globally present with epilepsy ranging from about 20 to 70 cases per 100,000 in a year and Over 85% of the epilepsy cases are present in underdeveloped and even developing countries with low or middle income. Two out of three of all epilepsy occurrences are genetic, with one percent familial and ninety-nine percent sporadic. A total of about Seventy-six genes has been associated with epilepsy and the variants in these genes are usually new or inherited.

Literature was obtained mainly from Public Medline with the use of search terms like “genetics of epilepsy”, “epilepsy”, “genetics and epilepsy”, “genetics”, epilepsy associated websites, and the NCBI.

Genetics has changed the clinical understanding of epilepsy and the reward is the provision of useful and vital information to the public at large and this has brought about interventions and breakthrough in the handling, care, treatment, diagnosis and control of epilepsy. Therefore, it is expedient that research on genetic mechanisms involved in epilepsy and the occurrence is encouraged and promoted as it will aid improvement in the knowledge of epilepsy and increase the ability to correctly diagnose the disease, and developing better treatment options.

Keywords: Genetics; Epilepsy; Seizure

Introduction

Genetics provides information about basic processes from birth till death, development to programmed cell death; and insight about disease aetiology and therapies as well as much better use of available treatments to solve underlined human health conditions because gene activity is involved with all biological process [1].

According to the International League Against Epilepsy (ILAE) [2], epilepsy, a common non-infectious neurologic disease remains a public burden. History wise, epilepsy was known to be a disease caused by the wrath from a higher being usually a god, devil, witch craft or an angry ancestral spirit [3]. The belief was that powerful entity such as gods, devil, witches, spirits could strip a man of his good and perfect health state, by propelling him up and down the ground, convulsing him and then restoring him to his former good state of health in a short while [3,4]. This historical knowledge has perpetually influenced the mind-set of the general public about epilepsy making it a feared disease as ‘lunatic’ was a term previously used to identify epilepsy patients.

In the Bible (St Mark 9 KJV), a foul spirit sent out of a man with fits and in Matthew’s account, the word epileptic was used to describe the boy. It is important to note that Jesus cast it out as he did to other demons, however the Bible eventually mentioned epilepsy as a condition different to demon possession in Matthew 4:24. These different beliefs have caused patients with epilepsy (PWE) to be castigated, ostracized and stigmatized. The social importance is negligible, for instance, in Madagascar, epileptics are refused burial in their different family allocated graves sites and even in some places in Nigeria [5].

In African countries, people with epilepsy are out-casts, as Africans have a deep and strong belief in history, and history according to Ogurinrin [3], says the disease resulted from visitation from the devil, witch-craft, ancestral spirit or consumption of dangerous substances. Epileptic individuals are likely to become drop outs, become jobless, find it impossible to marry, and becomes inflicted to the extent of becoming a wanderer [3,5] hence, suicide is common among epileptic individuals [2,3,5].

The WHO dictionary defines epilepsy as a recurring disorder of the central nervous system (CNS) of different aetologies which has a typical feature of recurrent seizures (the clinical manifestation of an abnormal and immediate synchronization of a population of cortical neurons leading to electrical activities in the brain) due to unconscionable discharge of cerebral neurons.

Epilepsy can be defined with any of the following conditions:

1. A minimum of two unjustifiable seizures happening more than twenty-four hours apart [6].

2. One reflex seizure with a chance of more seizures similar to the general recurrence risk of at least 60% after two unprovoked seizures, occurring over a span of 10 years [6].

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3. Presence of epilepsy syndrome [6].

There are many forms of epilepsy that can be distinguished by various characteristics including age of onset, predominant seizure type(s), and etiology [7]. Many factors can lower the threshold and trigger seizures such as flashing/bright lights, inadequate sleep, stress, sensory over-stimulation, certain medications, hyperventilation, alcohol consumption, fever among others [8].

Approximately 4% of individuals will develop epilepsy during their lifetime, making epilepsy one of the most common neurological conditions [9]. Given the relatively high prevalence and adverse effects on quality of life, epilepsy represents a substantial health and economic burden to the patients and the society [10]. The manifestation of epilepsy may be motor, sensory, psychic or autonomic, and exclude single afebrile episodes, febrile seizures, seizures due to altered metabolic states, seizures due to alcohol or drug withdrawal and other transient cerebral insults [11]. According to ILAE [12], three are three distinctive classes of epilepsies: which include Genetic classes, structural/metabolic classes and the unknown/uncategorized. It is important to note that genetic factors underline 70% of all epilepsy cases [8].

Prevalence of Epilepsy

About 50 million people are affected globally with a yearly incidence which ranges from 20 to 70 cases per 100,000 [13]. Over 85% of the cases are found in low and middle income nations. These incidence rates occur more within ages 15 and 65 years, and rises again among the elderly [13]. The prevalence is specifically high in underdeveloped and developing nations (Latin America and several African countries, such as Liberia and Nigeria) [2,3]. Most epileptic patients in African countries prefer to stay silent and are reluctant to open up about having the disease because of the stigma attached to the disease until it manifest publicly; this factor affects the prevalence rates hence a likelihood that most of the reported prevalence rates represent a fewer number, hence the chances of under-reporting are definitely high [12].

Reported epilepsy prevalence rates in Africa are based on selected communities and hospital admissions which range from 2.2 to 58 per 1000 [13]. Most African studies report a high case of epilepsy among males, this may be due to the fact that in most parts of Africa, males more readily go to the hospital for socio-economic reasons and hence predominate in the hospital populations and also, there is a higher prevalence of epilepsy among rural dwellers [3].

The figure (figure 1) below shows the commuted prevalence rate of epilepsy from 1988-2003 among various African countries, with lowest recorded prevalence of 3.5 in Democratic Republic of Congo, highest prevalence of 58 in Cameroon and an average of 15.83 in the total selected African countries.

Figure 1: Epilepsy prevalence among some selected African countries between 1988-2003 [16]

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One of the foremost publications on Nigerian epilepsy reported a prevalence between 0.8 and 1.3 per 100 people dwelling in the Lagos urban community; Osuntokun et al [14] reported a prevalence rate of 0.53 per 100 people among Igbo-Ora inhabitants. The prevalence rate is usually lower compared to rural African communities, and this low prevalence rate is due to the improvement in health functions and facilities. Another community-based study by Longe & Osuntokun [15] reported a prevalence rate of 0.62 per 100 among a rural Community of Udo, Nigeria. However, based on reported communities, the prevalence of epilepsy varies from 0.2 to 1.3 per 100 but with an approximated rate of 3.1 per 1000 [3]. These reports are vital as they show that, improved social health, general sensitization/awareness concerning epilepsy will reduce the incidence burden.

Pathomechanism of Epilepsy

The nervous system is the part of the animal that coordinates its actions by transmitting signals to and from different parts of the body via synaptic connections. This process is called synaptic transmission, which can be either excitatory or inhibitory [18]. The nervous system consists of two parts which include the (a.) Central Nervous System comprising brain and the spinal cord (b.) Peripheral nervous system (PNS) which according to Bourdenx M, et al. [21] mainly consist of nerves.

The nervous system is defined by presence of a special cell type – ‘Neuron’, which is also known as the nerve cell [22]. Neurons have special structures that allow them to send signals rapidly and precisely to other cells, these structures are known as dendrites [21]. Dendrites are branched structure of a neuron, where synapses are located (Figure 2). Synapses can be chemical or electrical, and the chemical synapses are more prevalent. They send these signals in form of electrochemical waves traveling along thin fibers called axons, which causes chemicals called neurotransmitter to be released at junctions called synapses [19]. According to Myers & Mefford; McTague et al. [19,22], thousands of
synapses, either excitatory or inhibitory, can be present in each dendrite and they can originate from multiple presynaptic neurons.

Dendrites are responsible for processing these synaptic inputs. Postsynaptic potentials are changes in the membrane potential at the synaptic terminal of the neuron that receives the signal. The postsynaptic potential generated by each active synapse is small, these excitatory and inhibitory postsynaptic potentials are, however, added together and if the sum exceeds a threshold, action potential is triggered.

Action potential is the electric signal that travels along the axon and sends information to other neurons [18]. In chemical synapses, the neurotransmitter that is released from the presynapse to the postsynapse via the synaptic cleft determines the nature of the synaptic potential. Gammaaminobutyric acid (GABA) is the most common inhibitory neurotransmitter where there is an inward flow of Cl\(^-\) currents, while glutamate and aspartate are examples of neurotransmitters in excitatory synapses where there is an inward flow of Na\(^+\) and an outward flow of Ca\(^2+\) currents. Other major neurotransmitters in the brain according to the American Epilepsy Society include acetylcholine, dopamine, serotonin, histamine and other modulators such as neuropeptides and hormones [18].

Classification of Epilepsy

Classification in epilepsy is primarily for clinical purposes. It influences every clinical consultation, yet its impact stretches far beyond the clinical domain to clinical and basic epilepsy research and to the development of novel therapies [27]. In 2017, the world’s main scientific body devoted to the study of epilepsy revised the classification of epilepsy. Figure 3 show a Framework for epilepsy classification according of international league of epilepsy.

According to the International League Against Epilepsy (ILAE) [12], there are three distinct aetiological classes of epilepsies: Genetic, Structural/metabolic and Unknown [17].

The genetic class of epilepsy was formerly referred to as idiopathic, implying that the underlying cause of the disease is unknown. Hildebrand et al., [8] concluded by estimating that genetic factors account for about 70% off epilepsy cases. Another report by Panayiotopoulos [29] shows that genetic generalised epilepsies (GGE) constitute the most frequent form of genetic epilepsies and it accounts for approximately 30% of all cases.

Epileptic encephalopathies (EE) are another subgroup of genetic epilepsies. They are individually rare but collectively account for an important fraction of epilepsies. EEs are early-onset and severe forms of epilepsies where epileptic brain activity contribute to cognitive and behavioural defects [17]. According to Khan & Al Baradie [30], epileptic encephalopathies do not respond well to antiepileptic drugs and they are associated with developmental delay or regression and poor prognosis. Genetic epilepsies can be further divided into epilepsy syndromes with distinctive electroclinical features and these can be arranged based on their onset (neonatal, infancy, childhood,
adolescence-adult) and characteristic findings in electroencephalogram (EEG) [17].

The second aetiologic category includes epilepsies that are caused by structural lesions or metabolic conditions [17] also known as symptomatic epilepsy. Structural defects, which increase the risk of epileptic activity, may arise due to acquired disorders such as trauma, stroke and infection. Notably, this category can also include genetic disorders, when the underlying genetic variants result in structural lesions or other defects causing seizures. Tuberous sclerosis is one example of such disorders. It is useful to note that symptoms are not always limited to seizures in many epileptic syndromes. The effect of the underlying causal factors is not often restricted exclusively on mechanisms regulating seizure activity but also other aspects of development and function of the central nervous system (CNS) and other tissues can be affected. Therefore, individuals with epilepsy may have other neurological symptoms, dysmorphic features, muscular disorders or other defects in any tissue [17].

The third aetiologic category includes epilepsies that are caused by unknown/uncategorized causes which cannot be categorically stated as having a genetic or symptomatic backbone [17].

The classification of Epilepsy according to Seizures

This classification includes the following

- Seizures beginning in the brain
  - Focal seizures previously referred to as partial seizures
  - Generalized previously referred to as primary generalized

- Seizures Describing Awareness.
  - Focal aware.
  - Focal impaired awareness.

- Describing Motor and Other Symptoms in Focal Seizures
  - Focal motor seizure
  - Focal non-motor seizure

- Unknown Onset Seizures Description

According to Brodie MJ, et al. [33], when the beginning of a seizure is not known, the classification still gives a way to describe whether the features are motor or non-motor.

Diagnosis of Epilepsy

Epilepsy diagnosis is still dependent on clinical information and evaluation [3]. Epileptic patients require the use of investigative modalities such as Electroencephalography (EEG) and neuroimaging facilities such as Plain Radiography, Computerised Tomography, MRI, Positron Emission Tomography. Other diagnosis method reported by DNA diagnostic experts [35] include physical examination, family history and genetic testing [36].

Electroencephalography is an electrophysiological technique that is used in monitoring and recording electrical activity of the brain. It is majorly non-invasive, and it uses a small metal discs known as electrodes attached to the scalp. It is mostly often used in epilepsy diagnosis. Despite limited spatial resolution EEG continues to be a valuable tool for research and diagnosis of epilepsy.

Plain Radiography generally refers to projectional radiography (without the use of more advanced techniques). It is also referred to as radiography that generates single static images as contrasted to fluoroscopy. Plain skull X-ray still has a place in developing countries although the development of advanced imaging techniques has made it almost irrelevant, although it is still very cheap, widely available and relatively innocuous despite its inferiority in both sensitivity and specificity to newer techniques). It is useful in the detection of bony changes (as seen in raised intracranial pressure and some tumours) and abnormal calcification (commonly associated with cerebral tumours, arteriovenous malformations and infections like cysticercosis, toxoplasmosis and cytomegalovirus) [3].

Computerised Tomography: It is also called CT scan and it makes use of computer processed combinations of so many x-ray measurements taken from various angles to produce many cross sectional (tomographic) images of the scanned area of an object, allowing the user to have an inside view of the object without cutting. It is also useful in detecting structural lesions and in determining the exact location of such lesions [37]. It is also useful in determining cerebral atrophy, a common abnormality demonstrated in epileptic patients [3].
Magnetic Resonance Imaging (MRI): This test makes use of magnetic fields and pulses of radio wave energy in making pictures of organs and structures inside of the body. This technique is much superior to CT scan [35].

Single Photon Emission Computerized Tomography (SPECT): This is an imaging technique that uses gamma rays. It is not commonly used in the diagnosis of epilepsy [38]. It is both a structural and functional neuro radiological investigation as it reveals the presence of structural lesions and metabolic disturbances. It makes use of radioisotope scanning to describe structural abnormalities and cerebral perfusion [3].

Positron emission tomography (PET): This is a nuclear medical imaging technique that is generally used to monitor metabolic processes in the body. It detects gamma rays indirectly emitted by a positron emitting tracer which is introduced into the body via a biologically active molecule [39].

Other diagnosis method includes:

Detailed information on clinical history gives insight to show if the seizure events are truly epileptic seizures, rather than non-epileptic events such as fainting, breath-holding, transient ischemic attacks, strokes, arrhythmias, or hypoglycemia, all of which show similarity to epileptic seizures [36].

Genetic testing: The information obtained from other diagnostic methods helps a clinician in determining if genetic testing should be offered to a patient with epilepsy and the particular genetic test (s) that is required or appropriate [35]. The outcome of a genetic test includes; positive, negative result, or a variant of unknown significance [40].

- A positive result shows the presence of the disease-causing mutation in the tested individual [40].
- A negative result does not necessary rule out a genetically inherited epilepsy syndrome in an epileptic patient [40].
- When there is indication that the pathogenic role of the variant cannot be clearly established, variance of unknown significance is reported [40].

Research on genetic mechanisms underlying epilepsy is essential for improving the knowledge, ability to correctly diagnose the disease, and also predict who will or will not end with epilepsy.

Management and treatment of Epilepsy

Dietary Management: research has shown that ketogenic diets are strongly linked with the management of intractable epilepsy. The classical diet is based on an estimated daily requirement of 75 kilocalories per body weight; 50% of the calories are given as fat, the remainder as protein and carbohydrates [12]. The fats are mainly long chain fats such as butter and cream [41].

Drug Therapy: Epilepsy diagnosis has a great implication to the sufferer, not least of which is the fact that the patient might likely have to be on medication for the rest of his or her life. According to [42] the administered drug can cause harmful side effects, and it requires continual medical supervision, therefore the decision to begin drug treatment requires rightful diagnosis of epilepsy, chance estimate of seizure recurrence, the extent to which anticonvulsant therapy will improve these chances be considered [3]. The most suitable drug for a particular type of seizure is selected and administered in a dose high enough to bring the plasma drug concentration within a therapeutic range without unacceptable side effects [32]. It is quite usual to find epileptic patients seeking alternative treatment methods in Nigeria [3,5,31] and this probably could explain late presentation in the hospital.

Surgical Management: Patients with frequent seizures despite good compliance with drug usage, good dietary management may require the surgical option [32]. According to a report by Mohamed et al., [43] the less seizures a patient has, the more easier it is to control the epilepsy, hence, ‘seizures may beget seizures’ has been hypothesized for more than a century.

Genetic Epilepsy

First gene discoveries in epilepsies were done in the 1990s. In 1990, the genetic defect underlying myoclonic epilepsy and ragged-red fibre disease, a syndromic form of epilepsy involving myopathy and spasticity in addition to myoclonic seizures, was identified in the mitochondrial genome [44]. In epilepsy syndromes where seizures are clearly the predominant clinical feature, the first causal variant was identified in CHRNA4, encoding a nicotinic acetylcholine receptor subunit [24]. This particular variant causes autosomal dominant nocturnal frontal lobe epilepsy. One of the most important gene discovered in epilepsy were variants in KCNQ2 and SCN1A, the former encoding a neuronal potassium channel and the latter a neuronal sodium channel [45,46].

International League Against Epilepsy [34] reported 76 epilepsy genes in total that have been identified and are all associated with different age groups (some identified with more than one age group) {49 genes identified among infants (0-12months), 31 genes identified among childhood (13months-12yrs), 13 genes identified with adolescents (13yrs-18yrs) and 9 genes identified among adults (over 18yrs)}, the types of seizures, and other associated features.

![Image](image-url)

Figure 6: Representation of genetic epilepsy [18]

Genetic Generalised Epilepsies (GGE) constitute the most common form of genetic epilepsies and it accounts for approximately 30% of all cases [29]. GGEs emerge typically in the childhood or adolescence and they are generally not associated with cognitive dysfunction or developmental delay. Seizures are generally well controlled with appropriate antiepileptic drugs in GGEs [29]. Epileptic encephalopathies (EE) are another subgroup of genetic epilepsies. They are individually rare but collectively account for an important fraction of epilepsies [30]. EEs are early-onset and severe forms of epilepsies where epileptic brain activity contribute to cognitive and behavioural defects [17].
Genetic epilepsies can be further divided into epilepsy syndromes with distinctive electroclinical features and these can be arranged based on their onset (neonatal, infancy, childhood, adolescence-adult) and characteristics findings in electroencephalogram (EEG) [17].

As mentioned earlier and illustrated in Figure 4, genetic factors underlie majority of epilepsies. The role of genetic factors in epilepsies has been formally demonstrated in family-based studies showing that relatives of affected individuals stand a higher risk of developing epilepsy and with twin studies further showing that monozygotic twins have higher concordance of epilepsy compared to dizygotic twins [17]. These reports confirm the role of genetics in epilepsy development.

Classification of Genetic Epilepsies

Mendelian epilepsies: Mendelian epilepsies causes a single gene to be missing or changed in which a single major locus accounts for segregation of the disease trait in a family and each is associated with a different age that the seizures start, the types of seizures, and other associated features [47,48]. There are few numbers of “idiopathic” mendelian epilepsies, such as benign familial neonatal convulsions and benign familial infantile convulsions, autosomal dominant nocturnal frontal lobe epilepsy, and generalised epilepsy with febrile seizures plus [39]. Epilepsies with mendelian epilepsies are rare but the risk to relatives are quite high.

Non-mendelian or “complex” epilepsies: This mutation occurs in a number of genes often coupled with environmental influence such as juvenile myoclonic epilepsy, where the pattern of familial clustering is accounted for by the interaction between several susceptibility loci and environmental factors. Example include entities such as childhood absence epilepsy and juvenile myoclonic epilepsy. This is further divided into - Mitochondrial disorders which result from mutations in DNA found outside the cell nucleus and – Epigenetic disorders: this disorders are related to changes in activity of genes in relation to the environment [48]. Common examples of complex epilepsies include juvenile myoclonic epilepsy [47]. Inheritance pattern in most epilepsies are usually non mendelian hence, risks to relatives are considerably lower.

Chromosomal disorders: chromosomal disorder particularly those involving autosomal chromosome imbalances cause the presence of a gross cytogenetic abnormality which are associated with CNS aberrations and other neurological variations [47]. An abnormality in chromosome 20 (R20) is a typical rare condition that causes epilepsy in children. Further examples include Miller-Dieker Syndrome, 18q-syndrome and 1p36 monosomy [48].

The family and beyond

If genetic factors are so important, why do most patients with epilepsy seem to lack an obvious family history of the disorder? At least two major scientific reasons account for this apparent paradox [49]. First, in complex disorders the proportion of affected relatives is much lower than is observed in Mendelian disorders. For example, in fully penetrant, autosomal dominant disorders (Figure 7), 50% of first-degree relatives are affected; whereas in complex disorders, typically less than 5–10% of first-degree relatives have the disease phenotype. Second, for epilepsies caused by de novo mutations, which are increasingly recognized to be important, no family history of epilepsy can be present by definition. However, a number of additional barriers can prevent a full appreciation of the importance of genetic factors in people with epilepsy [49]. These obstacles, for the most part, are created by failing to adequately ascertain the family history and by not appreciating the complexity of epilepsy genetics [38,49]. Obviously, inadequate inquiry into the wider family history will result in incomplete understanding; however, several potential pitfalls can be avoided.

Epilepsy, because of its intermittent nature and psychosocial consequences, is often covert. Seizures in the patient’s older relatives might not be disclosed, at least in part because of excessive social stigma [3]. This situation can be circumvented by asking about the family history at repeated intervals, and specifically asking the individual to speak to aunts and grandparents. Inheritance patterns are easiest to establish in excep¬tionally large pedigrees [46,49]. However, over-reliance on these rare examples, despite their being a valuable and necessary research tool, can discourage us from recognizing the existence of a familial history in a more modestly sized family (table 1) [24,48,49].
Autosomal dominant nocturnal frontal lobe epilepsy          AD          20q12.2          CHRNA
Generalised epilepsy with febrile seizures plus         AD1          9q13          SCN1B

Non-mendelian inheritance
Juvenile myoclonic epilepsy                          Complex          15q14          CHRNA
Childhood absence epilepsy (and/or EEG trait)         Complex          6p (EJMI)       Unknown
Juvenile absence epilepsy                            Complex          21q22.1        GRK1
Benign epilepsy with centrotemporal spikes            Complex          15q14          Unknown

Table 1: Major Genes implicated in genetic epilepsies [48]

<table>
<thead>
<tr>
<th>Genes involved in Epilepsy</th>
<th>Inheritance</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>SCN1B</td>
<td>1q19.1</td>
</tr>
<tr>
<td></td>
<td>SCN1A</td>
<td>2q24.3</td>
</tr>
<tr>
<td>Potassium</td>
<td>KCNQ3</td>
<td>8q24</td>
</tr>
<tr>
<td>Chloride</td>
<td>CLCN2</td>
<td>3q27.1</td>
</tr>
<tr>
<td>Calcium</td>
<td>CACNA1A</td>
<td>1p13</td>
</tr>
<tr>
<td></td>
<td>CACNA1H</td>
<td>1p13</td>
</tr>
<tr>
<td>Acetilcholine receptor</td>
<td>CHRNA4</td>
<td>20q13.2-q13.3</td>
</tr>
<tr>
<td>GABA receptor</td>
<td>GABRB2</td>
<td>5q34</td>
</tr>
<tr>
<td></td>
<td>GABRA1</td>
<td>5q34</td>
</tr>
</tbody>
</table>

Table 2: Common genes associated with the major ion channel

The different modes of inheritance can be found in the genes of epilepsy listed above, which includes: Autosomal, X-chromosomal, mitochondrial and complex inheritance. According to Thomas & Berkovic [49], family studies show that the age of onset, as well as the severity of the phenotype and the penetrance of these mutations is often less than 100%, and it varies within families.

Conclusion
Genetics is transforming clinical practice in epilepsy especially in children. The effect of the thorough understanding of the genetics of epilepsy that underpin both common and rare epilepsy have started to cascade into the clinical domain. Useful and beneficial information is hence being provided to individuals and the public, which has led to breakthrough in the correct management, treatment, diagnosis, control
and solutions to frequently asked questions on epilepsy such as I am pregnant with a male baby and am epileptic, will my baby be epileptic?

**Recommendation**

1. There is need for participation in genetic research on epilepsy as it is critical and essential for bridging the knowledge gap in epilepsy.
2. There is need for effective enlightenment and genetic screening and counselling centres for epileptic patients and their respective family members and even the public in general.

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