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The Genetics of Epilepsy: An Overview

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ABSTRACT: Approximately 50 million people worldwide are affected by epilepsy (PWE). India is home to about one-sixth of this population. In India, there are about 10–12 million persons with epilepsy (PWE). A sizable treatment gap (TG) exists because a sizable fraction of PWE does not obtain adequate care. Major causes of TG include low awareness of antiepileptic medicines (AEDs), cultural norms, the societal stigma associated with epilepsy, lack of access to healthcare, and critical scarcity of medical professionals with experience managing epilepsy. In this paper, an attempt has been made to provide a broad overview by stating the risk of genetic epilepsy, familial relationships and chances of genetic epilepsy, the etiology of epilepsy in India, importance of genetic testing for epilepsy with treatment options. India provides particular challenges in managing patients with epilepsy, not only in terms of the wide spectrum of epileptic conditions but also in demand for medical practice based on economic constraints.

KEYWORDS: Epilepsy, Treatment gap, Antiepileptic medicines, Cultural norms, Societal stigma associated with epilepsy, Healthcare, Scarcity of medical professionals

I. INTRODUCTION

The International League Against Epilepsy (ILAE) defines epilepsy as having two or more unprovoked seizures that happen more than 24 hours apart, one unprovoked seizure with a recurrence risk of at least 60% over the following ten years, or a recognizable epileptic syndrome (Beghi, 2020). Epilepsy (PWE), which the WHO estimates to affect 50 million individuals worldwide, is a widespread neurological condition (Cano, Fonseca, Ettcheto, Sánchez-López, de Rojas, Alonso-Lana, ... & Ruíz, 2021). PWE is spread primarily in low- and middle-income nations (80%). (LMICs). As a result, it is estimated that 10–12 million PWE live in India and are responsible for roughly one-sixth of the illness burden. According to the WHO, epilepsy caused 7,419,000 disability-adjusted life years and 0.5 percent of the global disease burden in 2015.

Estimates for India's prevalence and incidence range from 3.0 to 11.9 per 1000 people and from 0.2 to 0.6 per 1000 per year, respectively. Epilepsy instances are distributed differently based on socioeconomic class and geographic location, with males, rural areas, and lower socioeconomic status (Hirsch, French, Scheffer, Bogacz, Alsaadi, Sperling, ... & Zhou, 2022) exist with higher rates of the condition. The treatment gap (TG) for epilepsy in India is very wide. The proportion of PWE who are still untreated is referred to as TG. Reports state that the TG in India ranges from up to 90% in rural areas to 22% in urban areas. The TG is influenced by various factors, including a lack of knowledge about AEDs, cultural norms, societal stigma, indigenous treatment methods, and a chronic shortage of doctors with epilepsy management training. It is crucial to enhance care for those with epilepsy, given the higher prevalence of epilepsy and wider TG in rural areas. Untreated epilepsy can result in major injury and even death. Status epilepticus (SE) is a potentially deadly complication.

II. RISK OF GENETIC EPILEPSY

Several kinds of epilepsy, but not all of them, are significantly influenced by genetics (Abdel-Mannan, Taylor, Donner, & Sutcliffe, 2019). A person is said to have genetic epilepsy if they inherit a gene or a gene combination that increases their risk of developing epilepsy. As an illustration, some inherited metabolic and chromosomal disorders raise the chance of epilepsy.

But not all cases of hereditary epilepsy (Myers, Bello-Espinosa, Symonds, Zuberi, Clegg, Sadleir, ... & Scheffer, 2018) are passed down through families. In addition, unintentional gene changes sometimes bring on epilepsy. Epilepsy has been linked to various gene abnormalities that have been demonstrated to result in brain malformations.



Additionally, determining a person's genetic risk is not as simple as calculating $1 + 1 = 2$. For instance, despite having different gene mutations, two children may experience the same form of epilepsy. Or two family members may experience epilepsy and have the same genetic mutation, but their epilepsy syndromes may present differently. Varied forms of epilepsy have different inheritance patterns. Some forms of epilepsy are completely genetic in origin. Sometimes, a person's epilepsy diagnosis may include other factors besides genes.

The kind of epilepsy (focal, unknown or idiopathic, or generalized epilepsy), family history of seizure disorders and epilepsy syndromes, as well as environmental and other external factors, may all impact a person's chance of developing genetic epilepsy.

Traits of Patients Suffered from Epilepsy	Score
Family history of epilepsy	
Present	1
Absent	0
Mental decay	
Present	1
Absent	0
Sleep-wake circle	
No Seizures	0
Seizures during sleep stage	1
Seizure during wake stage	1
Seizures in whole sleep-wake	2
Multiple seizures type	
No Seizures	0
Only a seizure type	1
Two seizures type	2
Three seizures type etc.	3
Frequency of seizures	
No Seizures	0
A seizure occurring over a period exceeding a year (with AED) or onset	0.5
A seizure occurring between two months and a year (with AED)	1
One or more seizures less than two months (with AED)	2
MRI scanning	
Normal	0
Abnormalities	1

Traits of PWE with the score

III. FAMILY RELATIONSHIPS AND CHANCES OF GENETIC EPILEPSY

Frequently, epilepsy runs in families (Cursio, Ronzano, Asunis, Dettori, Cossu, Murru, ... & Pruna, 2022). The term "hereditary" refers to the genetic or physical characteristics that some members of the family share or that children inherit from their parents. Varied forms of epilepsy have different inheritance patterns.

According to one study (Ross, Stoyell, Kramer, Berg, & Chu, 2020), there is a 5% probability that someone would get epilepsy by the time they are 40 years old if either a parent or sibling has the condition. That is three times the risk faced by the ordinary populace. According to the research, a person may be somewhat more likely to inherit epilepsy if they have a family member with generalized epilepsy than if they have a family member with focal epilepsy. In the



case of identical twins, there is a very high chance that the other twin will also develop epilepsy if one twin has idiopathic epilepsy (epilepsy with an unknown origin).

Additionally, this can make people with epilepsy worry that they'll pass their seizure problem to their offspring. However, most kids born to parents with epilepsy do not go on to suffer seizures. The likelihood is less than 5% if the mother has epilepsy, but the father does not have the mother's epilepsy. The risk is a little lower if the father has epilepsy and the mother does not. The risk is only slightly increased if both parents suffer from epilepsy. A kid may get epilepsy between 9% and 12% if one parent has idiopathic epilepsy. There is always a chance that a child will acquire epilepsy because his family history of the condition can be a contributing factor.

IV. ETIOLOGY OF EPILEPSY

There are numerous potential causes for epilepsies (Garg, 2020); however, for up to 50% of affected individuals, a cause is unknown. In some instances, epilepsies have a definite genetic component, anomalies in brain development, infection, severe brain damage, stroke, brain tumors, or some other observable issue. Seizures can result from any condition that alters the regular pattern of neuronal activity, including sickness, brain injury, and abnormal brain development.

Etiology	Representative clinical conditions
Structural	Stroke, TBI, tumors, infection.
Genetic	Juvenil Myoclonic Epilepsy.
Infectious	Neurocysticercosis, tuberculosis, HIV, cerebral toxoplasmosis, cerebral malaria, postinfectious epilepsy.
Metabolic	Porphyria, aminoacidopathies or pyridoxine-dependent seizures.
Immune	Autoimmune encephalitis.
Unknown	Frontal lobe epilepsy.

Major etiologies of unprovoked seizures as well as epilepsy

A typical brain wiring, an imbalance in nerve communication in the brain (where some cells either overexcite or over inhibit other brain cells from transmitting information), or a combination of these variables may be to blame for the development of epilepsies. A typical brain circuitry in some juvenile illnesses leads to further issues, like intellectual disability.

Others may unintentionally create aberrant neural connections that cause epilepsy as the brain strives to heal itself following a head injury, stroke, or other issues. The growth of the brain can result in brain malformations and anomalies in the wiring that can disrupt neuronal function and cause epilepsy.

- **Genetics**

Certain epilepsies may emerge (Lindy, Stosser, Butler, Downtain-Pickersgill, Shanmugham, Retterer, ... & McKnight, 2018) as a result of genetic alterations. Numerous epilepsies strike several blood relatives, indicating a significant hereditary genetic component. In some situations, gene alterations that are referred to as "de novo" mutations can

happen spontaneously and contribute to the development of epilepsy in persons who do not have a family history of the condition. According to a study, hundreds of genes may contribute to the illnesses.

Mutations in the genes that code for ion channels, the "gates" that control the passage of ions into and out of cells to help modulate neural communication, have been related to several epilepsy types. For instance, a mutation in the SCN1A gene, which causes seizures by disrupting sodium ion channels, is present in most newborns with Dravet syndrome, a form of epilepsy characterized by seizures that start before the age of one year.

Additionally, progressive myoclonic epilepsies, characterized by repeated episodes of extremely rapid muscular contractions (myoclonus) and seizures, have been linked to genetic abnormalities. For instance, a gene that aids in the breakdown of carbohydrates in brain cells has been linked to Lafora illness, a severe, progressive kind of myoclonic epilepsy that starts in childhood.

Cortical dysplasia, also known as misplaced or improperly formed neurons, can result from mutations in genes that drive neuronal migration, a crucial stage in brain development. These incorrectly formed neurons can misfire and cause epilepsy.

Even though other genetic changes may not directly cause epilepsy, they may nevertheless impact the condition. For instance, one study found that many individuals with particular types of epilepsy have an unusually active gene that causes resistance to anti-seizure medications. In addition, by influencing brain development, genes may regulate a person's seizure threshold or vulnerability to seizures.

- **Other Disorders**

Epilepsies may arise due to brain damage brought on by various ailments (Truty, Patil, Sankar, Sullivan, Millichap, Carvill, ... & Aradhya, 2019) that impair regular brain function. Once these disorders are treated and resolved, seizures might stop. The likelihood of being seizure-free after the original illness is treated, however, is unpredictable and varies based on the type of disorder, the afflicted brain region, and the degree of brain damage that existed before therapy. The following are a few examples of ailments that might cause epilepsy:

- Hamartomas, benign brain tumors that develop as a result of neurofibromatosis and tuberous sclerosis complex, two genetic diseases
- Alcoholism or alcohol withdrawal
- Head trauma
- Alzheimer's disease
- Heart attacks, strokes, and conditions that deplete the brain of oxygen
- Arteriovenous malformations (abnormal blood vessel formation) or hemorrhage (bleeding in the brain)
- Inflammation of the brain
- Infections like HIV, meningitis, and viral encephalitis

Epilepsy may also be linked to cerebral palsy (Symonds & McTague, 2020) or other developmental neurological problems. Developmental neurological disorders account for about 20% of seizures in children. People with problems in brain development or other neurodevelopmental diseases frequently also have epilepsies. For instance, those with an intellectual disability or autism spectrum disorder experience seizures more frequently. In one study, a third of kids with autism spectrum disorder had epilepsy that was resistant to therapy.

V. IMPORTANCE OF GENETIC TESTING FOR EPILEPSY

Genetic testing (Oates, Tang, Rosch, Lear, Hughes, Williams, ... & Pal, 2018) aids in finding the origin of one's epilepsy. It might result in the best medical treatment and an accurate diagnosis. It might be especially beneficial for people with genetic epilepsy problems whose seizures are not under control.

Given that there are certainly known associations between specific medications and genetic epilepsy problems, in some circumstances, a genetic diagnosis may assist direct the choice of anti-seizure medications. There is evidence, for

instance, that some drugs may control seizures more effectively in individuals with a genetic diagnosis. Additionally, there is evidence that individuals with additional forms of genetic epilepsies¹⁻³ may not respond well to certain treatments or experience negative side effects.

A genetic diagnosis may occasionally be useful in determining the likely course of events. For instance:

- In some cases of genetic epilepsy, seizures may cease at a specific age, at which point a patient's doctor may determine it is safe to stop using anti-seizure medication⁴⁻⁵.
- Genetic testing results may improve family members' understanding of their own risk of epilepsy and their likelihood of becoming pregnant with an epileptic child.
- A genetic diagnosis can also provide doors to other resources for people and their families. These include peer families and advocacy groups' assistance.
- It might pave the way for involvement in studies focused on genetic diagnosis.
- The "diagnostic odyssey," or the quest for an explanation, might be concluded by receiving a diagnosis for a person or family.

VI. THE MOST COMMON GENETIC TESTING FOR EPILEPSY

The following (Fernández, Loddenkemper, Gaínza-Lein, Sheidley, & Poduri, 2019) are typical instances of genetic tests for epilepsy:

- **Epilepsy Gene Panel**
 - The most prevalent genes linked to epilepsy will be examined as part of this test.
 - Epilepsy gene panels come in a variety of varieties.
 - Some people have fewer than 20 genes, whereas others have hundreds.
- **Chromosome Microarray**
 - Chromosome analysis is part of this genetic test (structures that contain DNA).
 - Ensures there are no abnormalities that might result in epilepsy. Chromosome imbalances can include excess or missing sections of chromosomes or complete chromosomes.
- **Whole Exome Sequencing**
 - This intricate genetic test analyzes the complete DNA code to know changes in genes linked to epilepsy.

It examines a substantially wider number of genes, including uncommon and recently found genes, than the epilepsy gene panel.

- **Targeted Testing**
 - Other family members may undergo targeted testing to determine their risk if there is a recognized genetic cause of epilepsy in a person.

Some tests concentrate on chromosomes, gene families, or gene individuals. Multiple testing may be advised as no one test can diagnose all hereditary epilepsies. Testing may frequently be conducted in succession. Numerous laboratories offer genetic testing for epilepsies, and there is a significant difference among laboratories. For each of these factors, it is crucial that a medical professional who is familiar with genetic testing be engaged in the procedure.

Additionally, most genetic tests are carried out using DNA taken from a blood sample. A saliva sample or cheek swab sample may be used in several circumstances. A skin biopsy may occasionally be required.

VII. POSSIBLE RESULTS FROM GENETIC TESTING

A person's chance of having a genetic epilepsy disorder can be determined by genetic testing (Rochtus, Olson, Smith, Keith, El Achkar, Taylor, ... & Poduri, 2020).

➤ **Positive Test Result**

- A favorable outcome indicates a genetic variation has been found as the origin of the epilepsy diagnosis for the patient.
- An otherwise healthy person with a positive test may have an increased risk of developing epilepsy.
- Additionally, genetic testing may reveal reproductive concerns and show how epilepsy is inherited in a family.

➤ **Negative Test Result**

- A negative test result in an epileptic person indicates that the test did not reveal a genetic basis for epilepsy.
- Even a negative outcome does not exclude a genetic diagnosis.
- More testing might be thought of in some circumstances.

➤ **Uncertain Test Result**

- A genetic test could also produce unclear results.
- An unresolved result indicates a genetic finding was found, but its significance is unknown.
- The term "genetic variations of unknown significance" is used to describe these findings (VUS). When further information is available, a VUS result may be re-interpreted and re-categorized as benign (negative) or pathogenic (disease-causing/positive) later.

IX. TREATMENT OF EPILEPSY

The treatment plan (González, Yengo-Kahn, & Englot, 2019) for epilepsy depends on:

- the severity of symptoms
- health
- response to therapy

Some treatment options
comprise:

- **Antiepileptic (antiseizure, anticonvulsant) medications.** Antiepileptic drugs can lessen the frequency of seizures. They may stop seizures in certain persons. The drug needs to be taken exactly as a doctor instructs to be most effective.
- **Vagus nerve stimulator.** In order to stop seizures, this device is surgically implanted beneath the skin of the PWE chest and electrically stimulates the nerve that runs through the neck.
- **Ketogenic diet.** The ketogenic diet, which is high fat and low carbohydrate diet, is beneficial for more than half of children who do not react to drugs, claims the Epilepsy Foundation.
- **Brain surgery.** If PWE and a medical team decide it's the best course of action for illness, the part of the brain that triggers seizures can be removed or altered.

New treatments are still being investigated. Deep brain stimulation is one therapy that might become more readily accessible in the future. It includes inserting a generator into the PWE chest and electrodes into the brain. To lessen seizures, the generator sends electrical impulses to the brain.

The FDA approved deep brain stimulation in 2018 for use in adults over 18 with focal onset seizures who have not responded to at least three antiepileptic drugs.

Additionally being researched are radiosurgery and minimally invasive procedures.

X. CONCLUSION

An identifiable epileptic condition, one unprovoked seizure with a recurrence risk of at least 60% over the subsequent ten years, or two or more unprovoked seizures that occur more than 24 hours apart are all considered epilepsy by the International League Against Epilepsy (ILAE). Epilepsy (PWE) is a common neurological disorder that the WHO

estimates to afflict 50 million people globally. Genetics has a substantial impact on several types of epilepsy. Additionally, if a person inherits a gene or gene combination that raises their likelihood of having epilepsy, this is referred to as genetic epilepsy. For instance, some inherited chromosomal and metabolic abnormalities increase the risk of epilepsy. Often, epilepsy runs in families, and distinct kinds of epilepsy have different inheritance patterns. In addition, epilepsies have a clear genetic component, severe brain damage, abnormalities in brain development, infections, and more. At the same time, seizures can be caused by various conditions that affect the normal pattern of neuronal activity, such as illness, brain damage, or improper brain development. Therefore, genetic testing for epilepsy helps in identifying the cause of the condition, which may lead to a precise diagnosis and the optimal course of therapy, including antiepileptic drugs, a vagus nerve stimulator, a ketogenic diet, and brain surgery.

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