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# Epilepsy and Genetics

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## 1. Introduction

Epilepsy is one of the most common neurological disorder, that affects approximately 50 million people in the world and 90% of epilepsy cases are seen in the less developed countries[1,2].Epilepsy and seizures affect nearly 3 million Americans of all ages.Inheritance as etiology for epilepsy has been suspected for centuries. Despite the frequency of seizure disorder and epilepsy little progress has been made in understanding the genetics and physiological basis of epilepsy until the past two decades.

There has been strong evidence of genetic influence in some epilepsy syndromes from twin studies. The monozygotic twins have identical genotype and dizygotic twins are genetically similar like any two siblings and environmental factors are held to minimum in these studies. There is consistently higher concordance rates seen in monozygotic than dizygotic twins.The rates of concordance range from 10.8% in monozygotic twins with brain injuries to 70% in those without. In dizygotic twins the concordance rate is 3 to 10% [3,4].

Epilepsy is defined as recurrent unprovoked seizures[1].Seizures are unprovoked when there are no immediate precipitating factors (although an injury to the central nervous system may have occurred in the past) [5].Clinically epilepsy can be divided into two categories of seizure types: generalized and partial epilepsy. Generalized seizure refers to a condition when the entire brain is seizing from the onset of the event. Partial seizures describe condition when seizure activity starts from a localized brain region and has potential to spread to other areas of the brain.

The etiology of epilepsy can be divided into three categories, idiopathic, cryptogenic, and symptomatic. About 25% of epilepsies are associated with injuries to the central nervous system or gray matter like trauma, CNS infection, stroke, bleed, cerebral palsy, metabolic insults, etc. These types of epilepsy are classified as symptomatic according to the International Classification of Epileptic Syndromes. The remainder of cases are categorized as idiopathic or cryptogenic. The idiopathic epilepsies are of genetic origin. In the cryptogenic

syndromes a specific etiology is unknown. However, in many instances in the cryptogenic group a genetic influence may remain a possibility [6,7].

An important consideration is that epilepsy is often multifactorial and can be result of both external and internal contributions. Even in symptomatic epilepsies genetics may be a responsible or contributing etiology. Seizures are seen in number of congenital neurodevelopmental disorders with cortical malformations. Tuberous sclerosis (TS) is a type of neurocutaneous disorder with associated malignant childhood epilepsy. These children may have West syndrome (hyparrhythmia, mental retardation, and infantile spasm). About 50% of TS cases are familial and other half are sporadic mutation. It is a dominant mutation of two tumor suppressor genes TSC1 and TSC2 located on 9q34 and 16p13.3 that cause the disease [8].

Mutations in over 70 genes are found to be etiology for many types of epilepsy. Seizure is an episodic dysrhythmia of the cerebral cortex marked by abnormal network synchronization. Some of the inherited errors destabilize neuronal signaling by inflicting primary disorders of membrane excitability and synaptic transmission, whereas others do so indirectly by perturbing critical control points that balance the developmental assembly of inhibitory and excitatory circuits. Ion channels play a major role in generating and controlling neuronal excitability. The mutations of the ion channel can cause hyper- or hypo-excitability of neurons [9]. Usually channelopathies are associated with idiopathic epilepsy. Human inherited epilepsy disorders associated with ion channel mutations (Table 1) have been found in voltage-gated channels (Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, Cl<sup>-</sup>) and ligand-gated channels (nicotinic ACH receptors, GABA receptor) [10].

<b>Epileptic disorder</b>	<b>Voltage-gated Ion channels</b>	<b>Gene, locus</b>
Generalized epilepsy with febrile seizure plus type 1 (GEFS+)	Sodium channel, beta-1 subunit	SCN1B, 19q13.1
Generalized epilepsy with febrile seizure plus type 2 (GEFS+)	Sodium channel, alpha subunit	SCN1A, 2q24
Benign familial neonatal-infantile seizures (BFNIS)	Sodium channel, alpha subunit	SCN2A, 2q24
Benign familial neonatal convulsions	Potassium channel, alpha subunit	KCNQ2, 20q13.3 KCNQ3, 8q24
Juvenile myoclonic epilepsy Juvenile absence epilepsy Childhood absence epilepsy, type 3	Chloride channel	CLCN2, 3q27.1
<b>Epileptic disorder</b>	<b>Ligand-Gated Ion Channels</b>	<b>Gene, locus</b>
Autosomal dominant juvenile myoclonic epilepsy	GABA-A receptor, alpha 1 subunit	GABRA1, 5q34-q35
Autosomal dominant nocturnal frontal lobe epilepsy	Nicotinic acetylcholine receptor, Alpha-4 subunit	CHRNA4, 20q13.2-q13.3
Autosomal dominant nocturnal frontal lobe epilepsy	Nicotinic acetylcholine receptor, Beta-2 subunit	CHRNA2, 1q21

**Table 1.** Inherited epilepsy disorders and ion channel mutations.

Our knowledge in the field of epilepsy has evolved since the discovery of new specific inherited epilepsy syndromes. Causal mutations have been identified for some of these syndromes. They involve various ionic channels: Na<sup>+</sup> channels in the generalized epilepsy with febrile seizures plus (GEFS+), benign familial neonatal infantile seizure is another channelopathy associated with Na channel mutation, nicotinic receptors in autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), K<sup>+</sup> channels in benign familial neonatal convulsions, and GABA-A receptors in autosomal dominant juvenile myoclonic epilepsy. In addition, other paroxysmal neurological disorders like familial hemiplegic migraine and episodic ataxia a result of ion channel mutations and are sometimes associated with epilepsy [11].

More new genes associated with epilepsy has been reported the past several years and more mutations with electrophysiological information will emerge. The ion channelopathies linked to idiopathic epilepsies account for minority of cases. The ion channel mutation are common cause of rare monogenic idiopathic epilepsies [12]. The knowledge and understanding of genetics of epilepsy is growing rapidly perhaps with more detailed molecular dissection will have better definitions and explanation of the common epilepsy syndromes.

More and more genetic mutations are being found that contribute to development of epilepsy. Inheritance can be seen in the classical Mendelian fashion: autosomal dominant, autosomal recessive, X-linked or mitochondrial inheritance [13]. Familial epilepsies can be inherited in an autosomal dominant (AD), AD with an incomplete penetrance, or autosomal recessive (AR). Examples of mitochondrial inheritance include wider syndromes, such as “Mitochondrial encephalopathy, Lactic Acidosis and Stroke-like Episode Syndrome” (MELAS) and “Myoclonus Epilepsy with Ragged-Red Fiber Syndrome” (MERRF) [14].

However, in most cases the simple Mendelian model does not explain the familial distribution of most epilepsy. It is unclear how genetics and environment interact to influence the risk of developing different types or phenotypes of epilepsy syndromes. There is a large genetic influence in epilepsy perhaps the complexity stems from the fact that epilepsy is very heterogeneous, the important genetic and environmental factors may differ across clinically defined subsets or syndromes [5].

There have been familial genetic linkage studies conducted to understand genetics of familial epilepsy syndromes. Gene mutations have been found in multiple epilepsy syndromes including familial lateral temporal epilepsies, febrile seizures, generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy. Unfortunately, in many familial types of epilepsy genetic basis of the disease has not been identified including familial mesial temporal lobe epilepsy and photosensitive epilepsy [15, 16].

## 2. Generalized epilepsies

Generalized epilepsy with febrile seizures plus (GEFS+)

In 1997, Scheffer and Berkovic identified GEFS+ as a newly recognized autosomal dominant epilepsy syndrome [17]. They described a family that had 25 people with generalized epilepsy over 4 generations. Many individuals had febrile seizures past age 6 and/or had generalized afebrile seizures. The afebrile seizure types include atonic, myoclonic, absence and tonic-clonic seizures and in some partial seizures. Most phenotypes of GEFS+ have normal intelligence with normal neurological exam and normal brain imaging. In most individuals seizures stop by mid childhood and in some it persists. The genetic heterogeneity of GEFS+ has been well studied. The first locus was found on 19q13.1 (GEFS1) associated with gene (SCN1B) encoding sodium channel Beta 1 subunit. Missense mutations on SCN1A, found on locus 2q24, encoding for sodium-channel voltage gated alpha subunit account for most of the GEFS+ cases [18, 19]. Defects on SCN2A and GABA receptor subunit can cause the same or similar condition as well [4].

Febrile seizures are very common, about 5 to 10 % of children under age of 6 can be affected. The genetic cause of this is oligo- or polygenic rather than monogenic. There are rare autosomal dominant pattern identified and gene loci described. The gene locations include FEB1 on chromosome 8q13-q21, FEB2 on 19q, FEB3 on 2q 23-q24, FEB4 on 5q14a15, FEB5 on 6q22-q24 and FEB6 on 18p11.2 [20].

#### Autosomal Dominant form of Juvenile Myoclonic Epilepsy (JME)

This is a fairly common form of idiopathic generalized epilepsy. Patients with this disorder have early morning myoclonus and generalized tonic-clonic seizure. Age of onset is during adolescence. Patients have characteristic EEG showing generalized polyspike and wave discharges. Missense mutation of the gene GABRA1 encoding the alpha 1 subunit of the GABA-A receptor was recently found, locus 5q34-q35. This is not detected in the sporadic cases (21).

#### Childhood absence epilepsy (CAE)

Childhood absence epilepsy is a very common type of generalized epilepsy, making up about 8% of epilepsycases in school-aged children. The age of onset of seizures ranges from 4-13 years, with a peak at ages 6-7 years. There is family history of epilepsy in approximately 30% of patients. However, autosomal dominant pattern of inheritance with age-dependent penetrance is suspected. This is likely due to multifactorial pattern of inheritance involving interplay of the environment and genetics. The seizures are characterized by sudden impairment of consciousness lasting for several seconds. The EEG shows classic pattern of 3-Hz spike-wave discharge during the episodes [4].

One type of childhood absence epilepsy, ECA1, has been linked to 8q24, second type, ECA2, is caused by mutation in the GABRG2 gene on band 5q31.1. A third type, ECA3, is caused by a mutation of the chloride-channel gene CLCN2 on band 3q27. There have been reports of other epilepsy syndromes associated with voltage gated chloride channel mutation including, juvenile myoclonic epilepsy, juvenile absence epilepsy, and epilepsy with grand mal seizures on awakening [27]. The gene is CLCN2 which encodes chloride channel that is widely distributed in the nervous system and is involved in neuronal excitability.



### 3. Partial epilepsies

#### Familial nocturnal frontal lobe epilepsy

The genetics of this disorder was the first described for inherited idiopathic epilepsy. The age of onset for autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is adolescence or young adulthood. Patients have brief motor seizures during non-REM sleep. The typical duration of seizures are less than 20 seconds with brief awakenings. Patients may have more prolonged seizures. Patients usually complain of being tired during the day and underestimate the number of seizures. Auras are reported with these seizures including epigastric and sensory symptoms. A typical seizure may start with vocalization and grunting followed by hyper-kinetic movements or tonic contractions with clonic jerking. Treatment is with antiepileptic medication such as carbamazepine with reduction or cessation of seizures, but not all patients respond well to medication [4, 20].

First mutation in this disorder was identified in 1995, *CHRNA4*, and mapped to chromosome 20q13.3. More mutations and two other genes associated with this disorder (*CHRNA2* and *CHRNA2*) have been found; these genes encode alpha 4 and beta 2 subunits of the neuronal nicotinic acetylcholine receptor (nAChR), respectively. The nAChR is member of large family of ligand-gated ion channels [22].

#### Benign familial neonatal convulsions (BFNC)

BFNC is an autosomal dominant inherited epileptic syndrome that occurs in the newborns, onset within first days of life and spontaneously disappears within few months, at most fourth month of life. Patient has frequent brief seizures in the form of tonic stiffening, apnea, clonic, and focal movements. In rare cases adulthood epilepsy occurs, less than 10%. Although it was thought to be a generalized seizure at first, video EEG monitoring found the disorder is partial type of epilepsy [23].

Mutations in the voltage gated potassium channel genes have been identified in BFNC on chromosome 20q13.3 (*KCNQ2*) and more rarely on chromosome 8q24 (*KCNQ3*). More than 40 mutations have been reported for *KCNQ2* and three for *KCNQ3* [24]. Potassium channels are most critical for maintaining resting membrane potentials and enable rapid repolarization after an action potential. Mutations in either *KCNQ2* or *KCNQ3* decrease function of the encoded potassium channel.

#### Benign Familial Neonatal-Infantile Seizures (BFNIS)

This is an autosomal dominant epilepsy disorder characterized by focal afebrile seizures beginning age 2 days to 6 months and mean age of 11 weeks. The infants are normally developed. There have been 8 families reported to have this syndrome. Originally found in a large North American family. The mutation is in the sodium channel gene, *SCN2A* [25].

#### Benign familial Infantile Convulsions (BFIC)

This is another autosomal dominant inherited partial epilepsy syndrome. The seizures occur between 2 to 20 months and patient is in remission by age 3. Patient has clusters of afebrile

partial seizures over few days. Patients respond well to antiepileptic medication. This is a genetically heterogeneous disorder and linked to chromosome 1q23, 2q24, 19q and 16q12q12 loci. It was first described in Japan and then in Italy [26].

#### Non-ion channel genes in epilepsy syndromes

Most epilepsy genes mentioned above were associated with channelopathies. In 2001 it was found that non-ion channel genes play a minor role in etiology of idiopathic epilepsies. Autosomal Dominant Partial Epilepsy with Auditory Features (ADPEAF) or Familial Lateral Temporal Lobe Epilepsy (FLTLE) is a rare type of genetic epilepsy caused by mutation in the LGI1 gene (leucine-rich glioma inactivated gene 1) on chromosome 10q24. This mutation modulates excitatory neurotransmission. The clinical features of this disorder include complex partial seizures from the temporal lobe with auditory auras (identifiable voices, music, buzzing, roaring, and ringing), ictal aphasia, visual disturbance and secondary generalized tonic-clonic seizures. The age of onset is variable usually occurs in young adulthood. Usually the seizures can be well controlled on antiepileptic medications, some patients have spontaneous remission in their 30s and later [28,29].

#### Progressive myoclonus epilepsy (PME)

PMEs are collection of rare neurogenetic syndromes, and seizures are a predominant feature of these disorders. Patients usually have triad of myoclonic seizures, tonic-clonic seizures, and progressive neurological decline often associated with dementia and ataxia. The pathophysiology of these disorders is more diverse and mutations detected may affect many functions such as metabolic, mitochondrial function, and cell migration. Most PMEs are autosomal recessive in inheritance [30]. Examples of these disorders include Unverricht-Lundborg disease, Lafora body disease, myoclonic epilepsy with ragged red fibers, dentatorubral-pallidolusian atrophy, and neuronal ceroid lipofuscinoses.

#### Unverricht-Lundborg disease

Unverricht-Lundborg disease also known as the Baltic myoclonic epilepsy, because of its high prevalence in that region is a typical example of progressive myoclonus epilepsy. It is characterized by generalized seizures, myoclonus, and progressive neurological deterioration including dementia and ataxia. The disease was first described by Unverricht in Estonia in 1891 and by Lundborg in Sweden in 1903. The onset of disease is between ages of 6 and 18. It is autosomal recessive disease mapped on to chromosome 21q22.3. At this time few point mutations have been identified in the CSTB gene (Cystatin B). Cystatin B is found to be involved in normal maintenance of neuronal structure and loss of it in mouse models caused increased proteolysis, apoptosis, and gliosis [31]

#### Lafora body disease

Lafora body disease is a polyglucosan storage disease, first described in 1911 by Lafora and Glueck. It is an autosomal recessive disease; linkage to chromosome 21 and chromosome 6p23-25 have been found. The gene encoding novel protein tyrosine phosphatase called Laforin has been identified. Laforin is involved in development and maturation of neuronal networks [32]. This is a rare neurodegenerative disease most patients with this disease do

not live past their 20s. Onset of symptoms late childhood or adolescence and become progressively worse over time

#### Myoclonic epilepsy and ragged-red fiber disease (MERRF)

This is a mitochondrial disease that affects individuals before age of 20. Patients have ataxia, hearing loss, poor night vision, and myoclonic seizures. This is maternally-inherited mutation at position 8344 in the mitochondrial genome in over 80% of cases. Lactic acidosis and ragged-red fibers on muscle biopsy are diagnostic. Clinical presentation of mitochondrial disorders is very heterogeneous ranging from impairment in single tissue to encephalopathies, myopathies, cardiomyopathies and other complex multisystem disorders [14, 33].

#### Dentatorubral-pallidolusian atrophy (DRPLA)

DRPLA is a rare autosomal dominant disorder. The symptoms of this disease start in infancy to early childhood. The disease is from the trinucleotide (CAG) expansion on chromosome 12p. Patients presents with ataxia, myoclonus, dementia and seizures. The severity of the clinical manifestation depends on the length of the unstable trinucleotide repeat [34].

#### Neuronal ceroidlipofuscinoses (NCL)

NCL are autosomal recessive neurodegenerative disorders result in storage of lipopigments in brain and other tissues. It is a type of lysosomal storage disease. Clinical manifestation includes behavioral changes, seizures, visual problems, decline in mental function, and loss of motor function. There are different subtypes according to age of onset, pathology and genetic linkage.

Infantile NCL (CLN1) presents at about 12 months with developmental regression, myoclonus, ataxia, and visual problems. The genetic defect in CLN1 is identified in the palmitoyl-protein thioesterase gene (35). Late infantile NCL (CLN2) have similar clinical findings as CLN1 by age 2-4 years, patient may have intractable epilepsy. The gene found in most cases is in chromosome 11p15. Juvenile NCL (CLN3) also known as Batten disease is the most common neurodegenerative disorder of childhood. Clinical finding includes visual loss at age 5 to 10 years and gradual mental decline and seizures. CLN3 maps on chromosome 16p12.1. The CLN3 protein alters metabolism of proteins important for cell function. Adult NCL (CLN4) is a rare subtype and distinguished from others by absence of ocular manifestation. CLN5 and CLN6 are variants of the late-infantile NCL. [4, 36]

## 4. Pharmacogenetics and epilepsy

There is an inherited variance in drug sensitivity among patients; people react to the same medication differently. Pharmacodynamics and kinetic mechanism may be able to determine person's response to medication or adverse reaction. Genetic differences of receptor subunit may influence response to antiepileptic medications. Studies have shown that response to benzodiazepine can be genetically altered [37]. Current advances made in genetics can allow modulations of channel function. Targeting channels may be a successful way to



produce antiepileptic medications. Certain antiepileptic drugs affect different ion channels. Dilantin is an example of antiepileptic drug that inhibits voltage gated NA channel. There is hypothesis that alteration of the channel after mutation of a subunit may alter responsiveness to this medication [38]. However, some GEFS+ patients respond well to Dilantin so the mutation does not alter effectiveness of the medication. More systemic studies need to be completed to better understand this and this may be an important area of investigation [11].

Pharmacokinetics can affect drug resistance in epilepsy. Multidrug resistance (MDR) means resistance to structurally and functionally different agents. The MDR-1 gene encodes a membrane protein, p-glycoprotein, which functions to transport molecules across membranes. Increased expression of this is seen in brains of patients with intractable epilepsy [39].

## 5. Conclusion

As field of genetics of epilepsies continues to advance the genetic heterogeneity of epilepsy syndrome has become more apparent. There is heterogeneity in etiology and clinical manifestation of epilepsy[40]. In addition, different genes and mutations may cause the same seizure phenotype. The discovery of dysfunction of ion channels, channelopathies, account for many forms of inherited or idiopathic epilepsies as ion channels are critical for normal neuronal excitation. The progress made in understanding genetic of epilepsies will contribute to our ability to recognize and diagnose diseases, provide genetic counseling, potentially find new treatments and anticonvulsant medications.

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