

AN OVERVIEW OF THE GENETIC MECHANISMS UNDERLYING EPILEPSY.

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ABSTRACT

Epilepsy is a common neurological disorder. Although it has many causes including trauma, stroke, neoplasms and infections among others, there is evidence to show that genetics play a significant role in the molecular basis of manifestations of the epilepsy syndrome. Significant strides have been made recently in the field of epilepsy genetics in developed countries, this is yet to be replicated in the sub-Saharan region of Africa. This article seeks to highlight the genetic basis of epilepsy with the potential for improvement in the efficiency of epilepsy care in the context of individualised treatment. Furthermore, there is a need for more research to elucidate probable regional variations in the genetic mechanisms underlying epilepsy with the advent of next-generation sequencing (NGS) methods.

Keywords

Epilepsy, Genetics, Sub-Saharan Africa, Literature review

INTRODUCTION

Epilepsy is one of the most common neurological conditions affecting people of all ages.^{1,2} The term 'Epilepsy' is used to describe a family of neurologic disorders characterised by recurrent and unprovoked seizures. Some authors prefer the term 'the epilepsies' in defining these disorders that share an abnormality of increased susceptibility to seizures.³

The contribution of genetics to epilepsy could be traced to the Hippocratic writing "on the sacred disease" in 400 BC in which epilepsy was identified as an inherited condition.⁴ The epilepsy syndromes in which genes play a major role in their aetiology are generally referred to as idiopathic. This differentiates them from the 'symptomatic' epilepsy syndromes in which recurrent seizures are a component of a broader neurological disorder.⁵ This division is now controversial since there are genetic elements in some of the phenotypes previously classified as symptomatic.

The understanding of the molecular mechanisms underlying epilepsy is still incomplete.⁶ This becomes more challenging when an attempt is made to explain the role genetics play in these mechanisms. Genetic factors are the major determinants in at least 40% of all epilepsies and only 1% of these idiopathic epilepsies are inherited as pure monogenic disorders.⁷ These mostly mendelian and rare monogenic mutations have contributed significantly to the understanding of the genetic mechanisms of epilepsy. However, the mechanisms underlying most common epilepsies would likely involve an interaction of different gene variants (polygenic) in combination with environmental factors.⁷ These environmental factors include those peculiar to the individual which includes gender, age, hormones, and circulation rhythms and those

shared with members of the community including temperature, sound, and light.⁸

In humans, the environmental factors could be overt or subtle.⁹ The relationship between the genetic and environmental factors in epilepsy is complex and not fully understood. Also, the connection between climatic changes and epilepsy are likely to be multifactorial and indirect thus presenting challenges for predictability.¹⁰ The interplay between genetic and environmental factors in epilepsy can be buttressed by the fact that genetic mutations are expressed conditionally which could be subject to the environmental factor an individual is exposed to.¹¹

Notably, the introduction of the next generation sequencing is rather revolutionary and presents an opportunity for the implication of newer genetic mutations in the mechanisms underlying epilepsy.¹²

This involves new microarray oligonucleotide probe designer (MOPeD) in DNA sequencing which has revolutionized research involving the human genome. With these new technologies, the entire human genomes can be sequenced in one day, with the ability to sequence areas of interest or the whole genome. It also has a high sensitivity detecting mosaic mutations. However, it is currently not cost affective.¹³

The epilepsy burden in Africa is high and identifying the aetiopathogeneses has been a challenge. This is largely due to lack of resources (equipment and trained personnel) in these low and middle-income countries. It is therefore a necessity that Africa should benefit from the advancements in epilepsy genetics.

Although many genes have been associated with epilepsy, a handful of the genetic mechanisms underlying some selected epilepsy syndromes

would be discussed under various molecular processes.

ION CHANNEL MUTATIONS

Most of the single-gene mutations involve ion channels. There are two types of ion channels namely the voltage-gated channels and the ligand-gated channels.¹⁵ Both are important in the generation and propagation of neuronal signals. Voltage-gated channels are modulated by changes in the membrane potential while the ligand-gated channels are modulated by neurotransmitters which bind to a receptor site.

Voltage-gated ion channels for sodium (Na^+), potassium (K^+) and calcium (Ca^{2+}) consist of several subunits. These are the pore-forming unit, known as the α -subunit, and other accessory units which include the β , γ and δ subunits. The ion channel gates are normally closed during the resting potential. They open rapidly on depolarisation and remain inactivated with sustained depolarisation until a certain period of repolarisation. The fast activation of the Na^+ channels with relative inward Na^+ current accounts for the depolarization phase while the fast inactivation of Na^+ channels and activation of K^+ channels with relative outward K^+ current facilitate membrane depolarization. The Ca^{2+} channels are involved in the release of postsynaptic neurotransmitters, dendritic and somatic signalling, and in burst firing within the thalamocortical network. The neurotransmitters that activate the ligand-gated channels are either excitatory or inhibitory. Generally, acetylcholine and glutamate are excitatory while γ -amino butyric acid (GABA) and glycine are inhibitory. Any alterations in the functions of these channels may either enhance excitatory signals or reduce inhibitory signals resulting in increased susceptibility to seizures.

Sodium Channel mutations

Mutations in the genes that encode for sodium channels are seen in Generalised Epilepsy with Febrile Seizures plus (GEFS+).¹⁶ GEFS+ is mainly an autosomal dominant trait that presents with childhood febrile and afebrile seizures persisting beyond the age of six. A mutation in the *SCN1B* gene causing an abnormality of the $\beta 1$ subunit of the neuronal sodium channels has been linked to chromosome 19q13.1.¹⁷ This causes an interruption of a disulphide bond in a domain of the $\beta 1$ subunit.¹⁷ Mutations in the *SCN1A* and *SCN2A* gene affecting the $\alpha 1$ and $\alpha 2$ subunits of the sodium channels respectively have been described.^{18,19} Other disease loci for GEFS+ have been traced to chromosome 2q23-q24, 8q13-q21 and 5q22-q24.⁵ These mutations lead to impaired functioning of the sodium channels either by loss of function or gain of function effect. Both mechanisms have been reported to predispose neurons to hyperexcitability.^{17,20} It is not clear how these mutations cause epilepsy.

Another kind of epilepsy associated with sodium channel mutations is Severe Myoclonic Epilepsy of Infancy (SMEI) also known as Dravet Syndrome. It is associated with worrisome seizures that often present in the context of fever or illness. The onset is usually in the first year of life with declining psychomotor abilities noticeable in the second year of the disorder.²¹ Two types of mutations of *SCN1A* gene, de novo mutations and the mutations transmitted from mildly affected parents have been reported in patients with SMEI.^{22, 23} In a mouse model of SMEI, the hippocampal GABA-mediated inhibitory interneurons showed a selective loss of sodium current, causing an impaired inhibition with a predisposition to seizure development.²⁴ The symptoms and severity of SMEI could be

mediated by the degree of the loss of function effect caused by these mutations.²⁵

Potassium channel mutations

Benign Familial Neonatal Seizures (BFNC) is a rare autosomal dominant trait that presents with tonic-clonic seizures often appearing from the 2nd or 3rd day of life. The seizures mostly remit spontaneously. BFNC has a high penetrance and displays heterogeneity. The locus responsible for this disorder was localised to chromosome 20q and designated EBNI.²⁶ Analyses in two North American families identified another locus (EBN2) in chromosome 8q.²⁷ These were later named KCNQ2 and KCNQ3, respectively. The mutation in KCNQ2 is characterised by a deletion on chromosome 20q3.3 while that of KCNQ3 involves a missense mutation at chromosome 8q24 that affects an amino-acid in the pore-forming region of the potassium channel.²⁸⁻³⁰ These potassium channels are responsible for the M-type currents which act to moderate neuronal excitation.³¹ They are slowly activated and deactivated and play significant roles in repolarization. Hence, they determine the sub-threshold excitability of the neurons. Mutations in these channels may increase the excitability of neurons by causing a loss of function effect. Also, the fact that premature babies only develop the seizure when they have reached maturation shows the contribution development has in the expression of these channels and subsequent development of seizures.

Calcium channel Mutations

Alterations in the thalamocortical rhythms have been implicated in the pathophysiology of Childhood Absence Epilepsy (CAE).³ CAE is an idiopathic generalised epilepsy that is characterised by a three (3) hertz spike- and- wave pattern on EEG. Research using rat models of absence seizures have shown that three structural

elements of the thalamocortical network contribute to the development of generalized spike-and-wave patterns namely: the nucleus reticularis thalami, thalamocortical relay neurons and the cortex.³² The voltage-dependent calcium currents in the thalamic neurons are referred to as T-currents. An up-regulation of this T-type calcium current in the nucleus reticularis thalami has been reported.³³ Additionally, mutations in calcium channel genes encoding Cav3 channels (CACNA1G, CACNA1H, and CACNA1I) have been linked to epilepsy, other neurological and psychiatric conditions.³⁴ Ethosuximide and Valproate which are used for the treatment of generalised absence seizure block T-type calcium channels. These indicate that a gain of function caused by these mutations may be responsible for generalised absence seizures.

Mutations involving Acetylcholine receptors

Autosomal Dominant Frontal Lobe Epilepsy (ADFLE) is an example of focal epilepsy whose genetics involves mutations in acetylcholine receptors. In this disorder, seizures occur at night out of non-REM sleep. They occur in clusters and involve hyperkinetic movements with somatosensory or psychic auras usually preceding the seizures. It has a heterogeneous presentation even in the same family. An Australian study reported a mutation in a locus at chromosome 20q13.2 which is now known as the CHRNA4 gene.³⁵ This is a missense mutation (Ser280phe) that affects the $\alpha 4$ subunit of nicotinic Acetylcholine receptors.³⁶ Subsequently, another locus at chromosome 15q24 was reported to be associated with this disorder although no mutations were identified.³⁷ Two other missense mutations of the CHRN2 gene (val287leu and leu287met) located on chromosome 1q have also been reported.^{38, 39} These genetic loci are now known as ADFLE type 1, 2 and 3 respectively.⁴⁰

The exact biological mechanisms by which the above mutations lead to epilepsy are not clear. However, the val287met mutation in the CHRN2 gene (ADNFLE type3) has been shown to demonstrate a gain of function effect leading to an increase in acetylcholine sensitivity.³⁹ It is thought that this gain of function effect on the presynaptic nicotinic Acetylcholine receptors leads to the activation of inhibitory GABAergic interneurons. These interneurons which inhibit neuronal firing in the neocortex and hippocampus subsequently develop synchronous firing patterns involving an increasing number of pyramidal cells. This enhanced synchrony could lead to seizures after recovery from the inhibition.⁵

Mutations involving GABA receptors

GABA_A receptors are pentameric in nature and are inhibitory in the adult brain. They are closely related to the GABA_C receptors that function as chloride channels.⁴¹ Mutations in GABA_A receptors alter synaptic physiology. This alteration especially during fetal development and infancy may affect normal brain development and possibly lead to epilepsy.⁴²

GABA_A receptor channelopathies have also been associated with Childhood Absence Epilepsy (CAE). Feucht and colleagues identified a greater incidence of specific alleles of the $\beta 3$ subunits (GABRB3) among patients with CAE with the gene mapped to chromosome 15q11-q13.^{43, 44} This is the same region that is deleted in Angelman syndrome. Another mutation in the gene that encodes for the $\alpha 1$ subunit (GABRA1) has also been associated with CAE.⁴⁵ This mutation causes the deletion of a single base pair at position 975 of the $\alpha 1$ subunit. Other missense mutations that involve the $\alpha 6$ and $\beta 3$ subunits have also been reported.^{46,47} Mutations in the GABRB3 gene have been shown to give rise to

proteins with excessive glycosylation leading to reduced amplitudes in the GABA_A currents.⁴⁸ There is need for more explanations on how these alterations lead to epilepsy.

Two mutations of GABA_A receptors have been specifically associated with autosomal dominant juvenile myoclonic epilepsy (JME). JME is characterised by myoclonic jerks which mostly occur on waking up. They may also present with generalised tonic-clonic seizures and absences. The onset is within the second decade of life. The first mutation associated with JME is a GABRA1 missense mutation within the M3 transmembrane domain of the $\alpha 1$ subunit.^{48,49} A second mutation, GABRD, affects the extracellular domain of the GABA_A receptors.⁵⁰ These two mutations are associated with low amplitude GABA_A currents and reduced expression of the channels on the cell membrane.^{41, 49, 51}

NON-ION CHANNEL MUTATIONS

Mutations in the leucine-rich glioma-inactivated gene (LGI1) mapped to chromosome 10q23-24 were identified in families with autosomal dominant partial epilepsy with auditory features (ADPEAF).^{52, 53} A tandem repeat in the C terminal known as epilepsy-associated repeat (EAR) is common to both LGI1 and the monogenic audiogenic seizure-susceptibility gene (MASS1).⁵⁴ Mutations in MASS 1 gene were identified in a mouse model of audiogenic epilepsy⁵⁵ and subsequently, a human orthologue of this was reported.⁵⁶ Proteins produced from these mutations are thought to cause increased susceptibility to seizures by interfering with synaptic formation.⁵⁷ A putative receptor for LGI1, which has been linked to epilepsy, was identified in the ADAM22/stargazin protein complex in knock-out mouse models.⁵⁸ The LGI1 mutations may affect the interaction between LGI1 and ADAM 22 resulting in impairment of

synaptic transmission and development of epilepsy.⁵

GENETIC MUTATIONS ASSOCIATED WITH PROGRESSIVE MYOCLONIC EPILEPSIES (PMES) AND MALFORMATIONS OF CORTICAL DEVELOPMENT.

The PMEs comprise of a heterogeneous group of disorders that are characterised by a triad of myoclonus, tonic-clonic seizures and progressive deterioration of neurological function (including dementia and ataxia). Examples of this condition include Unverricht-Lundborg disease, Lafora body disease and myoclonic epilepsy with ragged red fibre (MERRF). The genetic aberrations that have been noticed in Unverricht-Lundborg disease and Lafora body disease would be discussed while that of MERRF would be discussed under mitochondrial mutations.

The Unverricht-Lundborg disease (ULD) is an autosomal recessive disorder with symptoms beginning between six and fifteen years. Mutations in the CSTB gene on 21q22.3 has been linked to ULD.⁵⁹ The CSTB gene encodes the reversible cysteine protease inhibitor called cystatin B which has a role in maintaining neuronal structure.⁵

Lafora body disease is a polyglucosan storage disorder that has an autosomal recessive pattern of inheritance. It is characterised by the presence of periodic acid-Schiff-positive intracellular inclusion bodies known as lafora bodies. Missense mutations in EPM2A, the gene that encodes for laforin, has been reported in Lafora disease.⁶⁰ Laforin is an enzyme that opposes the action of tyrosine kinases in cell signalling pathways. The loss of function created by this mutation leads to protein misfolding during genetic translation and might as well serve as the

molecular basis for the development of the disease.⁶¹

Mutations in various genes have been documented about cortical malformations, but the exact mechanisms by which these mutations cause refractory epilepsy seen in these disorders are still unknown.⁶² These malformations include focal cortical dysplasia, polymicroglia, lissencephaly and subcortical band heterotopia. Genetic and environmental factors regulate neuronal proliferation, migration, and organisation during development. Any disturbance in these processes has a potential to cause epilepsy and other neurological disorders.⁵ Also these mutations could lead to abnormalities in the neuronal microenvironment that predisposes to seizure (e.g. increased extracellular potassium and glutamate levels).⁶

MITOCHONDRIAL MUTATIONS

The mitochondria are involved in oxidative phosphorylation and cellular energy production. The mitochondrial DNA encodes transfer RNAs and messenger RNAs which produces proteins that are involved in the mitochondrial respiration. Mutations in mitochondrial DNA could affect these processes and subsequently give rise to pathological abnormalities. The mitochondrial genome is entirely inherited from the mother. Also, the distribution of mitochondrial DNA exhibits heteroplasmy whereby varying amounts of normal and mutated DNA populations are expressed in individuals and tissues. Two syndromes with mutations in mitochondria that are associated with epilepsy have been described. These are Myoclonic epilepsy with ragged red fibres (MERRF) and mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS).^{63,64}

Apart from the ragged red fibres and mitochondrial accumulation in muscle fibres, patients with MERRF would also present with progressive myoclonus and generalized tonic-clonic seizures.⁶³ The most significant is the mutation that involves an A to G transition at nucleotide pair 8344 in the mitochondrial tRNA gene for lysine.⁶⁴

MELAS is characterised by the presence of lactic acidosis and stroke-like episodes and it is often associated with epilepsy.⁶⁵ A point mutation at nucleotide pair 3243 affecting the dihydrouridine loop of tRNA gene for leucine was reported in Japanese patients with MELAS.⁶⁶ The exact mechanisms by which these mutations cause epilepsy are still unknown.⁶⁷

COPY NUMBER VARIATIONS

Copy number variants (CNVs) are duplications, insertions or deletions that affect regions of the genome. Currently, interest seems to be shifting from the common disease–common variant hypothesis to the rare variant–common disease hypothesis.^{68,69} This has become imperative with the inability of genome-wide association studies to demonstrate common variants associated with the more common sporadic forms of epilepsy.⁷⁰ The common disease – common variant hypothesis assumes that a set of common single nucleotide polymorphisms (>5% minor allele frequency) confer genetic risk to the disease.⁶⁸ In the rare variant- common disease hypothesis a large number of rare variants with significant effect is said to contribute to genetic susceptibility either individually or in different combinations in different patients.⁷⁰

Copy number variants as rare variants are the most common genetic cause of common epilepsies (i.e. the epilepsies seen frequently that do not have a strong family history and are not

part of another clinical entity).⁷⁰ CNVs have been associated with various neuropsychiatric conditions like autism, schizophrenia, learning disability and more recently epilepsy.⁷¹ A particular CNV could contribute to the genetic risk of developing various neuropsychiatric phenotypes and epilepsy. This pleiotropic phenomenon has raised the argument that these neuropsychiatric conditions and epilepsy may not be individual disease entities per se, rather, they may represent different phenotypic expressions of a shared neurodevelopmental abnormality.

Recurrent 15q13.3 deletions have been identified in unrelated persons with a variety of idiopathic generalized epilepsies.⁷² These deletions involve the region containing the ion channel gene CHRNA7. Recurrent deletions in 15q11.2 and 16p13.11, which have previously been associated with other neuropsychiatric disorders, have been shown to confer risk to the development of idiopathic generalized epilepsies.⁷³ Additionally, deletions involving 16p13.11 are associated with focal epilepsies.⁷⁴

Several propositions that need verification have been advocated to explain how a particular CNV could be associated with a range of phenotypes. These include the unmasking of recessive variants, epigenetic factors, environmental influences, mosaicism, and haplo-insufficiency.⁷⁰ Variable expressivity and to a lesser extent incomplete penetrance are also important in the explanation of the variable phenotypes associated with CNVs.⁷⁵ Much still needs to be known about these complex inheritance patterns and how these CNVs lead to the development of epilepsy and other neuropsychiatric conditions.

CONCLUSION

The role of genetics in the aetiopathogenesis of epilepsy has long been a topic of interest. Ion

channel mutations have contributed a great deal to the present knowledge of genetic mechanisms in epilepsy. Recent research on CNVs has given new hope to the genetic mechanisms of the common epilepsies. However, there remains a gap in the understanding of the role of epigenetic and environmental factors in elucidating the genotype-phenotype correlation. The advent of next-generation sequencing (NGS) with its potential for discovery of wider ranges of genetic variations has also opened up a new horizon and opportunities for the field of epilepsy genetics.

Although the perception of stigma in the context of the heritability of epilepsy seems to be improving, efforts should be made to educate patients on the advantages of undertaking an enquiry into the genetic mechanisms of epilepsy. These advantages include the likelihood of proper diagnosis and the possibility of making appropriate treatment choices.

Research in the field of the genetic mechanisms of epilepsy has mostly been done in resource-rich regions. It is recommended that collaborative research efforts should encourage more inputs from resource-poor regions.

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