ISSN 2521-0521

JOURNAL OF CONTEMPORARY PHARMACY

Volume 6: Issue 1: 2022

https://doi.org/10.56770/jcp2022615

Review article

SCN1A GENE MUTATION; A RISING CAUSE OF HUMAN EPILEPSY SYNDROME

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Submitted 1st November 2021, Accepted 7th March 2022

ABSTRACT

Epilepsy is found to be very common neurological disorder; it covers a wide range of abnormalities lying within brain. Generation of electrical activity of brain that is action potential and then its proper propagation in central nervous system (CNS) and Peripheral Nervous System (PNS) upto the target site is mandatory for the proper functioning of brain. The human sodium channel (SCN) family plays its critical role in all these neuronal mechanisms. These channels are prone to number of channelopatheis and mutations that are the key point of research and discussion now a day. About 700 mutations of *SCN1A* gene have been identified. This gene is considered as the commonly mutated gene in human epilepsy. This review is on the structural, functional and pathological aspects of SCN1A gene and its associated channelopathies. This will explore the advances in epilepsy genetics and may help in designing for new therapeutic modalities for treating epileptic patients.

Keywords: SCN1A gene, Epilepsy, Mutation, Dravet syndrome

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INTRODUCTION

Epilepsy is a chronic syndrome associated with other brain diseases. It is actually a collection of diverse neurological disorders which involve the unprovoked seizures. These unprovoked seizures are the sign of abnormal electrical activity in the CNS. Epilepsy is long-lasting illness that upsets the whole life of patient and make it dependent on medications for long time **[1]**. Seizures associated with epilepsy may come in several ways. It majorly depends upon the area of the brain that is affected and also on the age of the person **[2].** The most common type of seizures are convulsive seizures and they account for (60%) of total seizures. One third generalized seizures are due to the involvement of both hemispheres at the starting phase of epilepsy. Only one hemisphere is involved in two third of focal seizures which may convert into generalized seizures later. Other 40% of seizures are non-convulsive. Acquired epilepsy is about 20-30 %, causes may be head injury, brain tumor, toxicity of any chemical, drugs, genetic, anxiety, depression and hypoglycemia or any other cause. The remaining epilepsy about 70-80 % is admitted as due to genetic factor **[3].** The base of human epilepsy is human brain abnormality. It is due to the generation of abnormal impulses in the brain that majorly results from genetic mutations **[4].** Nearly 40% cause of this disease is unidentified **[5].** Unprovoked seizures are idiopathic. Idiopathic epilepsies are usually caused by genetic variations. Number of mutations may get responsible for these genetic variations in many unexplained genes **[6].** Epilepsy becomes more common with increasing age **[7].** There are about 10% chances for all people to have a seizure near the age of 80 years **[8].** In developed countries, infants and elderly people are more to get epilepsy while in developing countries the scenario is opposite. This is because of changes in the frequency of underlying causes **[9].** About 4% of people worldwide (65 million) have epilepsy **[10].** Each twenty eighth woman and twenty first man is getting disease of epilepsy **[2].**

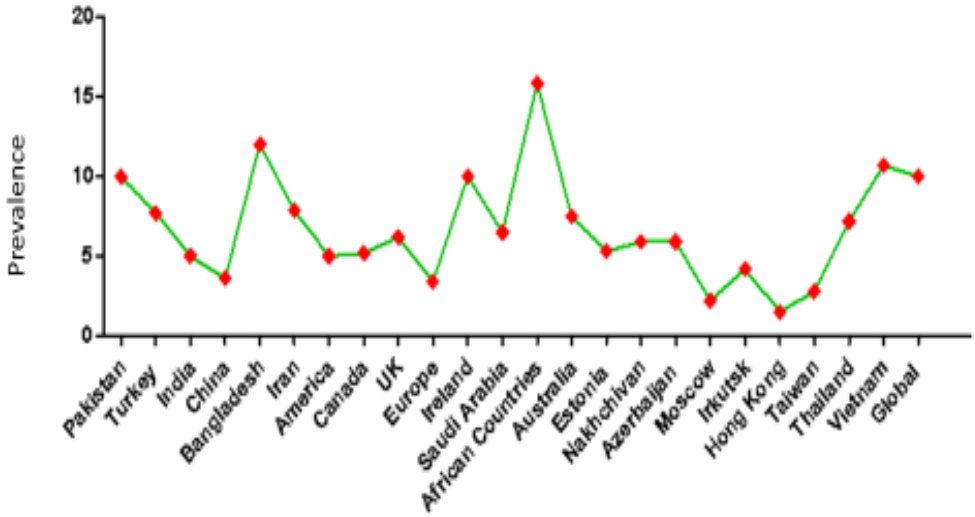

Figure 1: Country wise specific epidemiology/prevalence

DRAVET SYNDROME

It is disastrous babyhood epilepsy illness in which the seizures are usually related to intelligence debility and not responding to medicines. Dravet Syndrome contains marginal and conventional DS, wherein only a lot of clinical features are seen in the patients **[11, 12, 13].** DS is considered as general status epilepticus starting at the age of 6 month approximately, with other types of seizures, including myoclonic, partial, absence, and atonic seizures happening after passing the time of one year. In traditional DS, progress is postponed and patients every so often hurt from motor decline, as well as ataxia and spasticity **[14].**

Dravet syndrome (DS) has categorized by persistent seizures in the 1st year of an infant. DS develops to further types seizure like myoclonic and focal seizures, psychomotor delay, and ataxia **[15].** It is categorized by intellectual damage, behavior disorders, and motor deficits. It is also related with sleep disorders **[16].** The seizures beard by persons with Dravet syndrome convert into worst as there is no prediction of disease with the age of patient when first detected. This joined with the kind of severity different between each person detected and the seizures become drugs resistant made a challenge to improve treatments **[16]**.

GENETICS

It is analysed that epilepsy is caused due to abnormalities in number of unknown genes. These abnormalities most probably include gene mutations. Research has shown that these mutations are most frequently single gene mutations **[17].** In the majority of cases genes that are involved in epilepsy are those genes involved in ion channels. Although, the underlying defective mechanisms leading to epilepsy is not well comprehended **[18].** The electrical excitability is due to these channels. It looks that epilepsy is due to variation in the voltage gated sodium channels. Action potential of membrane motivates the channel and a change is done that depends upon voltage. Penetrability of sodium ions is amplified by the change in depolarization of membrane that outcomes in the more depolarization in the entire cell **[19].** After this depolarization ends in the inactivation and in the reaction of depolarization channel closed and penetrability to sodium ion is declined that outcomes in the rebuilding of the resting potential status. α subunit a highly treated nearly 260-kDa preparing sodium channel protein, that covers of four uniform and even domain named I-IV and each domain is needing six trans membrane parts recognized as S1-S6 **[20].**

Between the S5 and S6 a P-loop like hairpin sandwiched making a part of the channel pore and interrelating domain III and IV. An initiation door way is made by the formation of loop in the cell **[21].** Channels are connected in the mature central nervous system the channels are linked by β1,β3 and β2 β4 subunits. That are appeared in parallel style, so as the α subunits are related with the β1 or β3 and β2 or β4 **[11, 12, 13].** Each β subunit has a lone Trans membrane portion, an extracellular loop made of IgG-like and a C-terminus inside the cell. A subunits are bounded with β2 or β4 subunits via disulfide bond **[14].** Non-covalentlyβ1 or β3 subunits are linked with α subunit. The communication of β subunits with α subunit results in variation that make the α subunit kinetics, voltage

and localization dependent. Voltage-gated Sodium channel α subunit are coded by 9 genes in animal and human beings such as SCN1A, while SCN11A (SCN6A and SCN7A) presenting the same gene that encodes for the sodium non voltage-gated channel. Nine dissimilar isoforms are encoded by all these genes recognized as Nav 1.1 done withNav1.9 **[22, 23].**

In CNS 4 isoforms shows them at higher stages (Nav1.1, Nav1.2, Nav1.3 and Nav1.6) and (Nav1.6, Nav1.7, Nav1.8 and Nav1.9) 4 isoforms show them in PNS at higher stages elevated. Firstly (Nav1.4) in grown persons skeletal muscle (Nav1.5) in developing heart muscles and the residual 2 isoforms are appeared. In the course of the growth of CNS these isoforms are founded in miscellaneous sites **[24].** In the natal age Nav1.1 be an indication and grows up to childhood **[25].** There may be a stimulus of chemical or mechanical is changed into electrical impulses in the cells in their excited state via voltage-gated sodium channels **[26].** The formation of these channels by useful pore-farming α subunits and supplementary β subunits. Until now, 9 unlike forms of genes SCN (1-9A) are documented to encode the 9 unlike Na channels. Epilepsy related to inactivation of SCN2A and SCN1A **[27]** genes, SCN4A gene is related to myotonia disease, SCN5A gene is related to Brugada syndrome (OMIM 601144), young patients suffering with cardiac arrhythmias. Ataxia and cerebellar atrophy are disorders related to SCN8A gene. SCN9A gene is related to activating mutations and inactivating mutations unrelated with pain, with differing phenotype, hyperalgesia **[28].**

In the gestation period of fetal growth Nav1.2 acquires major level and in the maturity got at topmost level **[25].** Nav 1.3 acquires its topmost level of appearance at natal phase and generally undetectable in entirely grown individuals. Therefor it is declared as fetal isoforms [25] but it can be founded at lowest level of human beings maturity **[29].** Nav 1.3 is understood in NS of the matured rat afterward ANS damage of their dorsal root ganglion **[30, 31**] and in few rodents with epilepsy models **[32, 33].** Nav 1.6 displays that one appearance in the late fetal growth, initial perinatal **[34]** and adulthood phases **[35].** Nav 1.1 channel is founded abundantly in the area of spinal cord and matured CNS containing caudal reign while in rostral regions, positions of Nav 1.2 are full **[36].** Nav 1.1 is founded in the cell bodies and dendrites up to highest level **[37, 38].** It is mostly founded in the initial portion of axon for fast awkward parvalbumin positive neurons **[39].** Nav 1.2 abundantly existed in the dendrites and axons without myelin sheath **[37]**. Nav 1.6 is existed in the sensory and motor pathways and their sub-cellular dispersals existed in dendrites, axons, and cell bodies and post and pre-synaptic positions **[40, 41, 42].** Nav 1.6 is prime sodium channel at node of Ranvier **[42, 43].**

With their unlike sub-cellular dispersal and functional characteristics, each isoform for sodium channel is usually doing a vital job for beginning and transmission of action potential in membrane. For example, differentiating in matching to the earliest corner action potentials are motivated in the early portions. Due to effect of this propensity travel towards far most end is Nav 1.6 channels with extraordinary concentration in contrast to the amplified concentration of Nav 1.2 in the initial end, little beginning is for Nav 1.6 channels start **[44].** Early portion of parvalbumin-positive basket cells of axon wherever Nav 1.1 channels are existed in the clustered form **[39].** The completion portion of axon axle of parvalbumin -positive basket cells are scheduled nearby the activated neurons physically and early dendrites. The main task is to regulate the reactivity of all connection.

SCN1A

Humans protein which encodes by SCN1A gene (Sodium channel voltage-gated) is symbolized as Nav1.1, type I, αsubunit (SCN1A), Nav1.1 is named as neuronal voltage-gated sodium-channel also. To explain the concept of diseases with seizures and their reasons related to SCN1A the term is known as "channelopathies". Neuronal dysfunction is due to the molecular anomalies which in resulted in excitement of cortical network. SCN1A is an important part of gene group that encodes for Na channel. The location of this gene is 2q24 and making a cluster including SCN2A & SCN3A **[45].** Na- channel with Alpha subunit participate in the pore formation of membrane. A subunit having four domains with six transmembrane segments related with loops. S5 & S6 contains the remaining of pore lining and the P-loop which is discussed above related to S5 & S6. Residuum with positive charge which can be detected by voltage detector [15]. In all the segments of Nav1.1 having pathogenic variants which are related to epilepsy, they present up to in N-terminus also, in the voltage measuring device, the p-loops in D1-D5 and excessively present in C-terminus **[46, 47].**

Here are two kinds of epilepsy syndromes recognized. One is Generalized Epilepsy with Febrile Seizures Plus (GEFS+).and the other is extreme epilepsy of childhood, known as Dravet Syndrome or Severe Myoclonic Epilepsy of Infancy (SMEI) are in the results of mutations in SCN1A gene. The attacks (seizures) with pyrexia are known as GEFS+ is an autosomal (milder) highest hereditary epilepsy syndrome. The GEFS+ with

unlike kinds of its configuration in uninfluenced carriers, simple Febrile Seizures for most of patients, Febrile Seizures Plus and infrequently ample painful epilepsy. By the statements of scientists that all disreputable kinds of epilepsy genes and large number of variations epilepsy and hospital epilepsies are very much linked to SCN1A **[48].**

Nearly 10 % patients of GEFS+ are related with mutation in SCN1A gene and 85%patients of Dravet Syndrome are caused by mutations or removal of SCN1A. Approximately 30 SCN1A-GEFS+ mutations are recognized as yet. All missense mutations (replacement of amino acid) are there. All data is up dated regarding the functions of SCN1A but the work is continuously done to unveil the SCN1A mutations and their functions in the human body. In contrast, nearly half of above 600 SCN1A variations in Dravet Syndrome patients are due to frame shift, nonsense and splice site variations **[49, 50].** These mutations are present in a specific number too early in order of SCN1A, tough illuminating that after the changed allele a ornamental protein invention is a yield, or that show of the malformed allele is reduced, declarative of hap-lo-insufficiency of SCN1A **[51, 52].**

Common observation it is seen commonly that epilepsy in human beings is due to mutations in three of the genes that are coding for Na-channel α subunit, which are primarily presented in CNS. Many of the idiopathic forms of all the generalized epilepsies outcomes of mutation in SCN1A gene (Nav1.1) and SCN2A gene (Nav1.2). Genomic epilepsy as well as febrile seizures plus (GEFS+; MIM 604223) mostly in the outcomes of mutation in the two above said genes **[53-56]** SCN1B gene with mutation that encode for Na-channel β1 subunit **[57, 58]** and 2 GABAA receptors genes: GABRG2 encodes for γ2 subunit **[59-61]** and GABRD encodes for γ subunit **[62]** also causing for epilepsy syndrome. SCN1A mutations are the fundamental the basic cause of both back breaking early years epilepsy concluded tonic-colonic seizures generalized seizures, similarly named as severely generalized epilepsy with unknown reason of infancy also recognized as Dravet syndrome (DS, MIM 607208) **[40], [63].**

A few patients of DS and non-threatening inherited neonatal seizures (BFNIS; MIM 607745) are caused by SCN2A mutations **[64-66],** and it admitted that SCN1B mutations are responsible for painful Dravet syndrome **[67].** The mutation in SCN3A is causing focal epilepsy is seen in some studies (Nav1.3) **[68].** The mutations in SCN9A are admitted with febrile seizures in several years ago interestingly. SCN9A gene is harmonious to be linked largely in the PNS, SCN9A may work as a genomic modification of Dravet syndrome **[69].**

Gene Structure

SCN1A spans approximately 84 Mb of genomic DNA and has a transcript of 8,100 bp (reference sequence NM-006920.4). The gene comprises 26 exons that encode a protein of 1,998 amino acid residues (reference sequence NP-008851.3). Splicing variability has been reported. For a detailed summary of gene and protein information, 1.

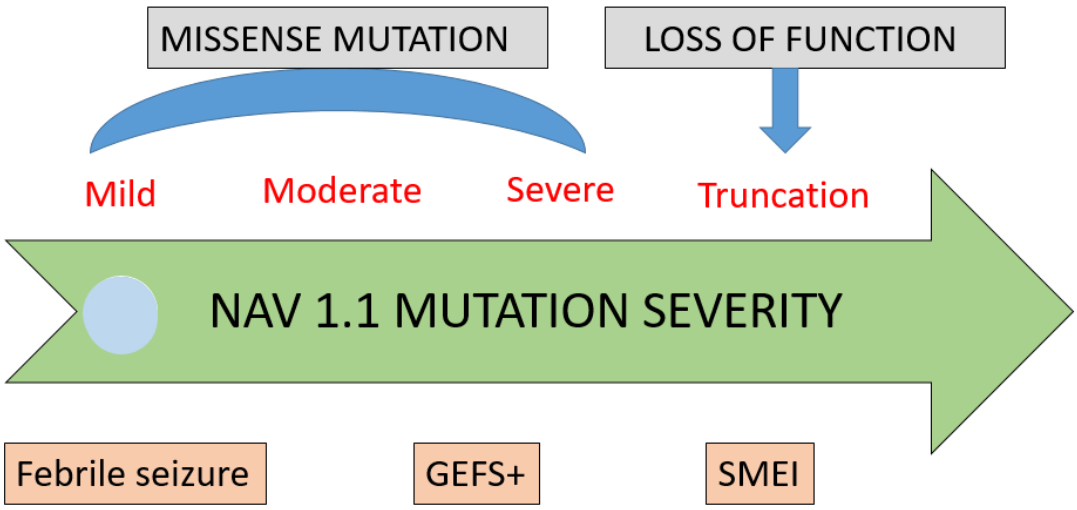

Figure 2: Spectrum of clinical phenotypes in SCN1A gene.

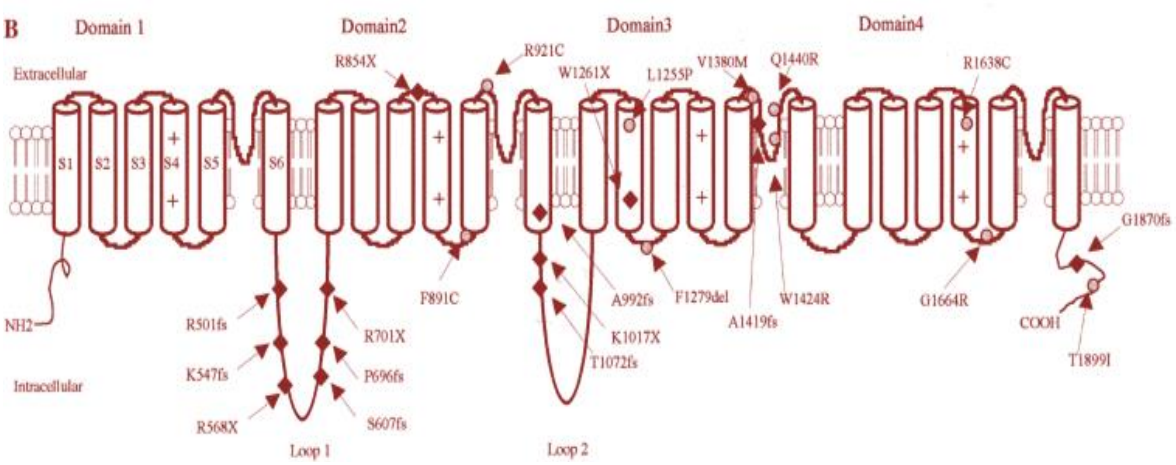

Figure 3: Domains and subunits of SCN1A gene responsible for epilepsy phenotypes.

Table 1: SCN1A-related seizure disorders genes and databases.

Gene	Chromosome Locus	Protein	Locus Specific	HGMD
SCN1A	2q24.3	Sodium channel protein type 1 subunit alpha	Familial Hemiplegic Migraine (FHM) Variation Database (SCN1A)	SCN1A

SCN1A Gene Conformation

The SCN1A contains eighty-four Mb of genomic DNA approximately and its transcription comprises of eighty-one hundred base pairs (reference sequence NM_006920.4). SCN1A gen has 26 exons which are encoding for the construction of 1,998 AA remainders long protein (reference sequence NP_008851.3). Splicing mutation is described in some studies **[51].**

A several number of missense mutations in SCN1A gene are accepted in DS cases. Due to several missense mutations there may also halt the character of channel, may be altering the physical features of the channel, relationships with new particles or shifting or subcellular localization. Approximately all DS mutation are de novo in pediatric patients, while in the affected families with GEFS+ mutations are not as in DS patients. It is mentioned in the recent studies that almost all de novo mutations repetitively start from the fatherly chromosome **[70].**

The comparison between various cycles of mitoses in the development of spermatozoa with the development of ova and disposition of the sperm cell's DNA with methyl group to acquire mutations are able to prove the above statement. But most of the DS cases hold from beginning of SCN1A variations, approximately instances have been described them the mutation was inborn and from a slightly affected or without symptoms parental was genetic. In a large number of patients having germ line and somatic SCN1A mosaicism is described **[71-74].**

Authentication of SCN1A Mutation

Firstly, to regulate whether there are any predictable useful significances connected with alteration / mutation and secondly, to attempt feature this changed role to the detected clinical signs and symptoms of epilepsy are main goals of useful authentication of SCN1A gene modifications. This will come to be clear that although for a several number of variations of SCN1A for the 1st goalmouth that has been completed, the 2nd probably more energetic goal has verified difficult to achieve. Here is no comprehensive mechanism attainable that can explain how the level of supposed useful properties linked with epilepsy agreed with cases possessing this nutation to date. Special effects exposed by human SCN1A mutations effects on human being are shown on ion channel properties were mostly described by presenting them in extra derivative of human Na-channel subunits gene which may be described beyond of β in addition subunits. In rat, it is expressed in Xenopus oocyte beyond of β as additional subunits **[75-78].**

Although, the adjacent demo of appearance of changed human SCN1A derived in neural tissue **[79].** In the cloning of human beings, the arrangement of SCN1A is mildly changed, 3 generalized epilepsy with febrile seizures plus variations takes place as well as extra β subunits, in other mammalian cells were completed by themselves.

The mutations are R1648H and T875M **[48]** and W1204R **[50].** Epileptogenesis is implication for fundamental mechanism which is derived from the

presentation of these mutations is damage of functions at minor level along with continuous extra activity of neurons in the excited state and internal Na- current. The situation become more complicated while studying extra 5 mutations (four GEFS+ and one SMEI) **[80].** Two GEFS+ patients (11656M of **[51]** and R1657C, (which had not been formerly reported), they recognized changed gating qualities of an operational channel. The qualities are understood in three previous evaluated mutations of there is no result on Na-currents or disability **[79].** In difference, the A1685V GEFS+ allele of, the V 1353LGEFS+ allele of **[81],** and the L986F SMEI allele of **[82]** displayed whole deficiency of function **[80].** Accordingly, as considered in this appearance scheme, only disability of SCN1A mutations is not accrediting for the clinical difference amongst SMEI and GEFS+ **[83].**

They assumed multiple associations of the biophysical possessions of channel with genetic modifier and metabolic, that is only channel characteristics performed not be a predictor of phenotype. SCN1A gene is very sensitive regarding functions in the atmosphere of cell disadvantaged for the studies. In the discussions of the earliest studies, their oocyte and HEK293 expression is used as a proof of SCN1A production channel with different degrees of sensitivity to β extra subunits unlike dynamic properties.

Useful level of channels is summarized by the alterations in transcription or shifting can be able to resolve these changed functional influences and display a basic key in relating mutations with the phenotype of the patient, in the membrane of cells. Further means to incorporation the extensive range of useful effects to a general phenotype are reserved together with a particular representative study by **[84]** who used computer for reproducing to an collection of mutation with several efficient effects. There is a validation that a variety of mutation, all of one with a miscellaneous degree of useful variations can be all yield a hypothetical increase in cellular volatility as strong-minded by an enhanced speediness of action potential gunfire by means of a standard.

Instead of any infrequent variant directly linked to the actual mutation will continually isolate with the sickness, which is not related to their importance of its functional. Exclusion of the expected mutation in large cohort of families is much important than when observed in smaller cohort families, but, in infrequent size families liable alleles with smaller significances will not ever be seen isolating. In the condition in which the mutation expected to having a pathogenic result changes an AA at a site in the protein conserved by development, or a site conserved into proteins encoding the alike gene family, this will be a strong incidental proof that the mutation is pathogenic. The most valuable condition for decision of pathogenicity was created on evolutionary conservation that distributes the strong provisional proof, earlier to the duplicating of human appearance conceptions of SCN1A **[69].**

DIAGNOSIS

The identification of disease is intensely depending upon bodily investigation of patient and clinical history of disease. It is very problematic to discriminate between epilepsy and seizures. The start of the first seizure having significant values in the diagnosis of disease. Info's regarding starting time of seizure, promoting factors of seizures and circumstances should be composed. Epilepsy is often not diagnosed. Thus the mandatory diagnosis is differential diagnosis e.g., arrhythmias, non-epileptic seizures, and unconsciousness. Best investigation to diagnose the epilepsy is EEG, but patients having normal EEG are not safe from epilepsy. EEG can give adequate information of classification of epilepsies. Ictal EEG results adding further information in the diagnosis of epilepsy. MRI is another helping investigation to evaluate the epilepsy. It is providing better help to the diagnosis of epilepsy.

TREATMENT

We can get rid of genetic epilepsy through rule out the genetic cause also. For evaluation of the cause we collect blood samples of epileptic patients. After extraction of DNA sequencing is done to identify the causative mutations SCN1A gene mutations are notorious for genetic epilepsy. We can see the SCN1A gene mutations in patients with family history of epilepsy. Treatments of epilepsy are anti-epileptic drugs (AEDs) are commonly given. These treatments are used for long durations with maximum side effects. There is a need of proper care at efficient level.

CONCLUSION

There is enormous advancement in the field of molecular genetics. Ion channel genes belong to the gene family that is most frequently affected and mutated causing a number of brain disorders including epilepsy. Studies on the pathophysiology and mechanisms of their channelopathies might open new corridors towards better treatment options, which may be helpful in identifying the exact defects. Along with this, the advancement in the knowledge about mutated genes can help in designing of new drugs targeted to specific pathogenic mechanisms.

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