Genetic basis of pediatric epilepsy syndromes (Review)

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Received June 13, 2016; Accepted March 21, 2017

DOI: 10.3892/etm.2017.4267

Abstract. Childhood epilepsy affects ~0.5-1% in the general population worldwide. Early-onset epileptic encephalopathies are considered to be severe neurological disorders, which lead to impaired motor, cognitive, and sensory development due to recurrence of seizures. Many of the observed epilepsy phenotypes are associated with specific chromosomal imbalances and thus display gene dosage effects, and also specific mutations of a variety of genes ranging from ion channels to transcription factors. High throughput sequencing technologies and whole exome sequencing have led to the recognition of several new candidate genes with a possible role in the pathogenesis of epileptic encephalopathies. The mutations causing channelopathies can be either a gain or a loss of ion channel function and contribute to the pathogenesis of epilepsy syndrome. Nearly 300 mutations of SCN1A gene coding for the Nav1.1 channel protein have been identified that contribute to the pathology of epilepsy. Besides Na, potassium and calcium channels are also implicated in epileptic encephalopathies. Therapeutic management of epileptic encephalopathies has been challenging as the majority of the medications are not efficient and often have many undesirable side effects. A better understanding of the molecular nature of epilepsy in an individual is important to design a personalized medication, considering the number of possible genetic mutations that can contribute to epileptic encephalopathies.

Contents

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Key words: childhood epilepsy, epileptic encephalopathies, neurological disorders

1. Introduction

Childhood epilepsy is a common neurological condition and affects ~0.5-1% in the general population, with an approximate total of 50 million people worldwide (1). Early-onset epileptic encephalopathies are considered to be severe neurological disorders, which lead to impaired motor, cognitive, and sensory development due to recurrence of seizures. It has been recognized that many of the observed epilepsy phenotypes are associated with specific chromosomal imbalances and thus, display gene dosage effects, which are of significant interest to understand the specific roles of the involved genes and their cognate protein products (2). Therefore, information on the chromosomal abnormalities related to epilepsy likely reveal the underlying mechanisms for various epilepsy phenotypes, including fragile-X, trisomy 12p, Wolf-Hirschhorn, ring 20, and 1p36 deletion syndromes. Even though the role of genetic factors in idiopathic epilepsies has been suggested for a long time, the involvement of genetic factors has been clearly demonstrated in cryptogenic and symptomatic epilepsies (3). Nearly 40% of the etiological causes for epilepsy are now known to be due to genetic factors (4). However, Mendelian epilepsies seem to account only for 1% of epilepsies, implicating non-Mendelian inheritance of some of the affected genes. Interestingly, the estimated risk of epilepsy for off-springs and siblings of epileptic patients was found to be only 2-5% (3). In fact, advanced next-generation high throughput sequencing technologies, have led to the recognition of several new candidate genes that may play a role in the pathogenesis of early-onset epileptic encephalopathies (5,6).

The role of environmental factors in genetic epilepsies cannot be discounted, even though the major determining factor for the seizures is the underlying mutation, since the environmental factors can influence the expression of such genetic defect, phenotypically either aggravating it, or even dampening it (7). On the basis of genetic complexity, there appear to be two types of epilepsies: i) The Mendelian epilepsies, which are generally monogenic, simple, and rare and account for ~1% of all epilepsy cases (8) and ii) complex epilepsies, which affect the majority of the patients, are common and multigenic. Several studies have suggested that genetic and environmental factors interact to different degrees and thereby influence the susceptibility to epilepsy (9). Mendelian epilepsies include monogenic syndromes with single gene defects causing the specific phenotype (9) and often show variable penetrance and severity and these also include the majority of cases of Dravet syndrome [severe myoclonic epilepsy of

infancy (SMEI)], caused by *de novo* mutations (10). The monogenic inheritance of epilepsy syndromes include autosomal, X-linked, and mitochondrial types, although most common epilepsies display complex or polygenic inheritance (11). Some epilepsy syndromes, such as epileptic encephalopathies, involve intractable seizures in association with intellectual decline, and include Lennox-Gastaut syndrome, myoclonic astatic epilepsy of Doose, and Dravet syndrome (12). Epileptic encephalopathies can be due to acquired etiologies or structural abnormalities of the involved proteins like ion channels or they may be because of specific gene mutations affecting neuronal excitability. Increased understanding of the molecular and genetic insights of these syndromes hold promise for designing disease-specific therapies.

2. Chromosome 18 abnormalities in epilepsy

Nearly 500 different chromosomal abnormalities have been described to be associated with disturbed EEG patterns and seizures. Certain chromosomal abnormalities show a greater association with epilepsy, e.g., Wolf-Hirschhorn (4p-), Miller-Dieker (del 17p13.3), Angelman syndrome (del 15q11-q13), inversion duplication 15, and ring chromosomes 14 and 20, while many others show weaker associations (13). Rearrangements of chromosome 18 have been observed in some patients; however, due to the lack of complete details on the epilepsy it is difficult to draw precise genotype-phenotype correlations. Nevertheless, patients with trisomy or duplication of chromosome 18 were found to display high incidence of epileptic seizures with a prevalence of up to 65% (14). Children with 18p-deletion, show an anomaly as they have less frequent epileptic seizures but poor seizure control. On the other hand, patients with 18q-deletion syndrome also suffer from epilepsy with predominantly focal seizures, which are well controllable and occurring during early years of life. Among all the abnormalities of chromosome 18, 18q-deletion syndrome and full trisomy 18 are described to be frequently associated with epilepsy. Patients with trisomy 18 show both partial and generalized epilepsies, with onset in the first year of life (13).

3. Channelopathies

Several ion channels are essential for proper maintenance of neuronal excitability and these include voltage-gated sodium, potassium, and chloride ion channels and ligand-gated acetylcholine receptor and γ-aminobutyric acid subunit-α receptor-mediated ion channels. Mutations in the genes coding for these ion-channel components lead to ion channel dysfunction, also known as channelopathies, which are the basis of the development of several epilepsy syndromes (15). The mutations causing channelopathies can be either a gain or a loss of ion channel function and contribute to the pathogenesis of epilepsy syndrome (16,17). Benign familial neonatal seizures (BNFS) have been found to be associated with mutations in the genes KCNQ2 and KCNQ3 that code for M-channel subunits of voltage-gated potassium channels, present in the central nervous system (18). A mutation in either the α4-subunit (CHRNA4) or the β2-subunit (CHRNB2) gene of the neuronal nicotinic acetylcholine receptor are known to cause the partial seizures associated with autosomal dominant nocturnal frontal lobe epilepsy (19). More common are the mutations that affect the function of sodium channels such as voltage-gated sodium channel, type 1 (Na_v 1.1) and lead to the epilepsy syndromes in children (20).

Sodium channel mutations. Na_v channels, which exist in three different functional states (open, closed and inactivated states) are responsible for the initiation and propagation of neuronal action potentials (21). At rest, Na channels are in closed conformation and no sodium current flows. Upon membrane depolarization, the channel opens with a rapid influx of Na^+ ions into the neuron. The Na^+ ion current peaks in <1 msec and falls back in few milliseconds. Soon after opening, the channels are closed by a gating mechanism to prevent continuous membrane depolarization. There are 9 subtypes of Na channels (Na_v 1.1 1.1-Na_v 1.9), and Na_v 1.1, which is encoded by the SCN1A gene, is densely distributed in the initial segments of axons in the brain, the site of generation of action potentials (22,23). Na channels regulate the action potential output of the neuron, which also determines the excitability of neighboring neurons. Thus, Na channels influence not only the overall excitability of neural networks but also of the individual neighboring neurons. Therefore, an imbalance in the excitation and inhibition in the Na channel operated neuronal excitation can lead to uncontrolled neuronal firing, hyperexcitability, and seizures. Linkage analysis of an Australian pedigree spanning 4 generations, comprising generalized epilepsy with febrile seizures plus (GEFS+) syndrome (24) led to identification of a mutation in SCN1B, on chromosome 19, which codes for the β1-subunit of the Nav1.1 channel (25). This mutation, which causes a tryptophan for cysteine substitution disrupts the formation of a putative disulphide bridge in the extracellular immunoglobulin G loop of the β-subunit, thus causing accelerated Na current flow through the Na channel and thus membrane hyperexcitability (26).

Subsequent studies identified several mutations in SCN1A and SCN1B genes of Na channels causing channelopathies (27) in patients with GEFS+ (Fig. 1). Apparently, only ~10% of the families with GEFS+ display mutations in the SCN1A gene, which are missense mutations, with single amino acid substitutions. Besides GEFS+, mutations in SCN1A have also been observed in almost 80% of the patients with SMEI, where these mutations occur *de novo* (28). In patients with SMEI, 40-67% of SCN1A mutations are nonsense or frame-shift types that cause truncation of the coded protein. Missense mutations of SCN1A gene are ~30-40%, whereas ~20% mutations are deletions and splice site mutations in SMEI (28). Thus, SCN1A mutations can lead to a broad spectrum of epileptic syndromes (Fig. 1) ranging from mild (GEFS+) to severe (SMEI), with the intermediary borderland clinical syndromes, depending upon the type of mutation, with truncation mutations being most severe and missense mutations that cause single amino acid substitutions being less severe (29). It is evident that patients with Na channelopathies should not be administered with Na channel blockers for any other indication, as these drugs can worsen their situation. At present, genetic testing for these mutations is highly expensive and not readily accessible, even though it is desirable to be available for routine clinical testing of the affected patients.

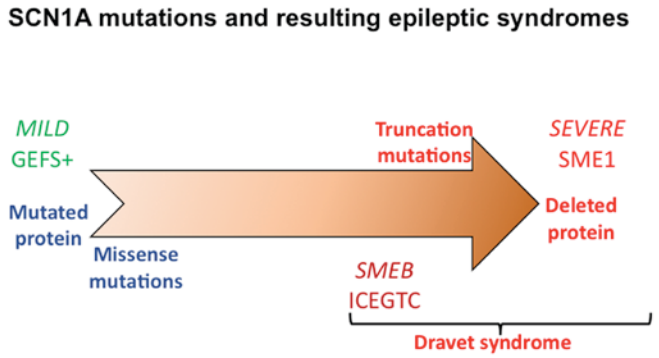

Figure 1. SCN1A mutations resulting in epileptic syndromes. SCN1A mutations, that cause single amino acid substitution, which are mostly missense mutations, lead to mild clinical epilepsy as in generalized epilepsy with febrile seizures plus (GEFS+). Deletion mutations that cause either truncation of the protein or total loss of expression of the protein cause severe intractable epilepsy such as severe myoclonic epilepsy of infancy (SMEI). Epilepsy syndromes of intermediate severity are seen in severe myoclonic epilepsy borderland (SMEB) and intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC). Together, SMEI, SMEB, and ICEGTC are part of Dravet syndrome.

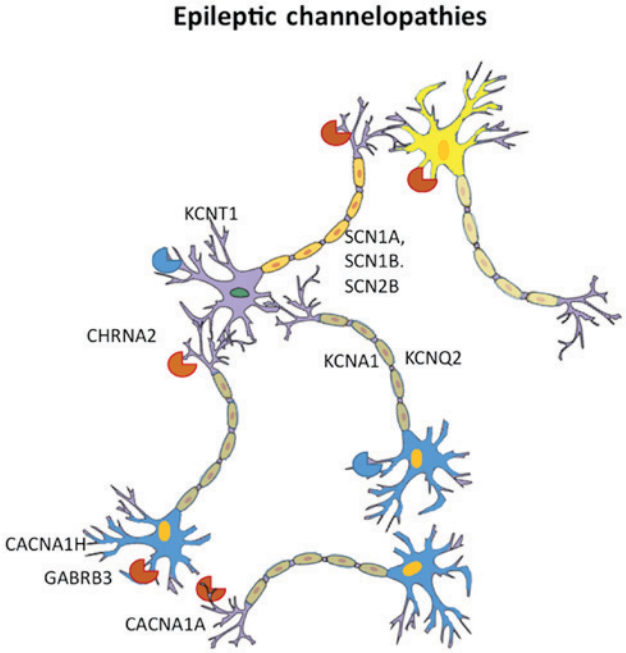

Figure 2. Epileptic channelopathies. Some of the identified ion channels, whose mutations are implicated in the development of epileptic seizures are shown in this scheme. Among these Na channels (SCN1A, SCN1B and SCN2B) are well studied and established for their role in epilepsy.

Pathogenic heterozygous mutations in another gene, SCN8A, which codes for a 1980 amino acid Na channel protein (Nav1.6 subunit) that is involved in membrane depolarization during the generation of action potentials in neurons and also in muscles (30), are also found to cause both early onset epileptic seizures and intellectual disability without epilepsy. It has been found through whole exome sequencing that majority of the SCN8A mutations are *de novo* and display a wide clinical pattern that includes multiple seizure types, intellectual disability as well as developmental retardation following the onset of seizures (31).

BFNS. BFNS are clusters of seizures, which appear within the first few days after birth up to the third month and disappear spontaneously, with a 15% risk of seizures appearing later in life (32). Most patients suffering with this form of epilepsy syndrome have mutated KCNQ2, the gene encoding the voltage-dependent K+ channel, KQT-like subtype member, and deletions/duplications involving one or more exons of this gene (32). Mutations in the associated gene KCNQ3, voltage-dependent K+ channel, KQT-like subtype member 3 are seen in relatively fewer families (17). *In vitro* studies revealed that heteromeric wild-type and mutant KCNQ2/3 channels, when coexpressed show a ~30% reduction in the potassium current, which accounts for the development of BFNS (33). However, it is not apparent why these seizures are seen only in neonates and it is speculated that this may be due to higher susceptibility of neurons in neonatal brain and/or because of possible replacement of the mutated channels in the later stages of growth (34). Mutations in other ion channel protein coding genes including KCNB1 gene that encodes the KV2.1 potassium channel (35), KCNT1 gene that encodes a sodium-activated potassium channel (36), CACNA2D2 gene, encoding for an auxiliary subunit of high voltage-gated calcium channels, which is involved in the regulation of the protein trafficking and, subsequently, of neuronal calcium current influx (37), and the HCN1 gene that encodes a hyperpolarization-activated cation channel (38), have been found to be associated with different forms of epilepsy (Fig. 2).

Benign familial infantile seizures are similar to those observed in BNFS, but have an age of onset ~6 months (39), and these patients display mutations of the PRRT2 gene, at the pericentromeric region of chromosome 16, and also suffer from familial infantile convulsions, paroxysmal kinesigenic or exercise-induced dyskinesia, migraine, or hemiplegic migraine, or in various combinations (40,41). However, the location or the type of mutation of PRRT2 gene do not appear to affect the severity of the disease (41). PRRT2 codes for a protein that interacts with a synaptosomal membrane protein involved in Ca^{2+} triggered exocytosis.

4. Non-ion channel genes and epileptic encephalopathies

Even though the majority of epileptic syndromes have been found to be associated with mutated ion channel proteins, few non-ion channel proteins are also found to be involved in epileptic syndromes. PCDH19, which is part of the protocadherin delta-2 subclass of the cadherin super family and expressed mostly in the nervous system, where it plays a role in neuronal connections, is found to be mutated in an X-linked epilepsy and mental disorder that affects only girls (42). Other cases of non-ion channel genes that are implicated in epileptic syndromes include: Aristaless-related homeobox gene, on chromosome Xp22, a transcription factor that belongs to a family of paired class homeobox genes and involved in the nervous system development (43); X-linked gene cyclin-dependent, kinase-like 5, mutations of which cause severe myoclonic form of epilepsy (44); and syntaxin binding protein 1 gene, mutation of which is associated with Ohtahara syndrome or early infantile eplileptic encephalopathy (45).

Recent whole exome sequencing studies revealed many other genes that are found mutated in different forms of

epileptic encephalopathies. Most of these mutations have been thought to arise as *de novo* mutations or are inherited in an autosomal recessive fashion, as compound heterozygous mutations (31). Mutations of these new genes, which are associated with different forms of epilepsy phenotypes, are found in a limited number of cases and sometimes resemble the known syndromes, including Dravet syndrome (46,47).

5. Management of epilepsy syndromes and therapeutic approaches

There are several significant co-morbid features associated with epileptic encephalopathy and these include the loss of language or other cognitive or developmental abilities, behavioral and attention deficits including autistic-like features, psychiatric problems, and sleep disorders (48). Management of epilepsy is often challenging, and requires treatment of not only the seizures but also the other frequently associated disabling co-morbidities. Unfortunately, the conventional anti-epileptic medications are far from effective in most patients. However, few drugs appear to be promising in specific cases. Thus, vigabatrin is found to be quite effective in West syndrome, if caused by tuberous sclerosis. But this drug has a major drawback as it poses the risk of vigabatrin associated visual loss (49). Among other medications, valproate and lamotrigine are considered as a first-line treatment in Lennox-Gastaut syndrome (LGS) (50). Also rufinamide use in a randomized controlled trial in LGS patients led to a marked reduction of seizures (51). Clobazam is frequently used to treat Dravet syndrome and LGS patients. Benzodiazepine therapy may have a risk of worsening tonic seizures in LGS patients. Sulthiame, a carbonic anhydrase inhibitor, which acts via Na channels has also been used in some forms of epilepsies (52). Besides these drugs, corticosteroids have been used in childhood epilepsies but only a small proportion of patients respond to this therapy (53,54). Interestingly, ketogenic diet, which consists of high ratio of fat to carbohydrate, has been found to be efficacious in reducing multiple forms of epilepsies and it has been suggested that use of this diet early in infancy may be more effective (55,56). However, the mechanism by which ketogenic diet offers this protection from seizures is not known yet. In patients who are resistant to pharmacological interventions, surgery is often considered as a palliative option. Patients with focal or hemispheric lesions might improve in response to surgical treatment, such as lobectomy, hemispherotomy, or hemispherectomy, particularly in earlier stage (57,58). Advances in cell biology will likely help in future in the use of induced pluripotent stem cells, to correct the genetic defects that lead to the various forms of epileptic syndromes. However, this approach is still in the lab and may take some time to reach the clinic.

6. Conclusions

Early-onset epileptic encephalopathies are severe neurological disorders, which lead to impaired motor, cognitive, and sensory development. Several chromosomal abnormalities and gene mutations, particularly those coding for ion channel proteins have been implicated in the pathogenesis of epileptic encephalopathies. High throughput sequencing technologies and whole exome sequencing have led to the recognition of several new candidate genes, besides those coding for ion channel proteins, with a role in the pathogenesis of epileptic encephalopathies. A significant quantum of study has been done on the role of SCN1A Na channel coding gene in the pathogenesis of different forms of epilepsy. Despite the identification of several players, an effective therapy for epilepsy is not yet available and the currently used medications suffer from unwanted side effects. Corticosteroids and ketogenic diets have been found to be better in managing epilepsy, when implemented early in life. Breakthrough in genetic engineering and gene editing technologies and stem cell applications should hopefully lead to a better therapy for epilepsy not far from now.

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