Review

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Inherited Epilepsies

Kalıtsal Epilepsiler

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ABSTRACT

Mutations in genes encoding the formation of ion channels may cause epileptic syndromes. These epileptic syndromes are generally divided into generalized and partial epilepsies. Among the causative agents of generalized epilepsy showing mendelian or non-mendelian inheritance; mutations in sodium channel, calcium channel, GABAA receptor and nicotinic receptor can be listed. Generalized epilepileptic syndromes with mendelian inheritance are Genetic Epilepsy With Febrile Seizures Plus, Autosomal Dominant Juvenile Myoclonic Epilepsy, and Epilepsy Associated With *CLCN2* Gene Mutation. Generalized epileptic syndromes with non-mendelian inheritance are JME and Juvenile Absence Epilepsy With Generalized Tonic-Clonic Seizures. The epilepsies of newborns and infants with a single gene inheritanceare classified into three categories: Benign Familial Neonatal Convulsions, Benign Familial Infantile Convulsions, and Benign Familial Neonatal-Infantile Seizures. Autosomal dominant partial epilepsies are examined under the headings of Autosomal Dominant Nocturnal Frontal Lobe Epilepsy, Familial Mesial Temporal Lobe Epilepsy, Familial Lateral Temporal Lobe Epilepsy, and Autosomal Dominant Partial Epilepsy With Auditory Features. While various mutations in different ion channels can produce similar phenotypes, a certain mutation on the same gene can cause different phenotypes. This review provides a summary of the epilepsy classification on the genetic basis and pathophysiological effects of neural channelopathies causing epileptic syndromes.

Keywords: Epilepsy, channelopathies, inherited epilepsy, genetic mutations

ÖZ

İyon kanallarının oluşumunu kodlayan genlerde meydana gelen mutasyonlar epileptik sendromlara neden olabilir. Bu epileptik sendromlar genel olarak jeneralize ve parsiyel olarak ikiye ayrılmaktadır. Kendi içerisinde mendelyan ve non-mendelyan geçiş gösteren jeneralize epilepsilere neden olan etkenler arasında sodyum kanalı, kalsiyum kanalı, GABAA reseptör ve nikotinik reseptör mutasyonları gösterilebilir. Mendelyan geçiş gösteren jeneralize epilepileptik sendromlar; febril nöbetler ile karakterize, otozomal dominant formlu juvenil miyoklonik, *CLCN2* gen mutasyonuyla ilişkili, kalsiyum kanalı alt birimlerindeki mutasyonlarla ilişkili epilepsiler şeklinde farklılaşmaktadır. Non-mendelyan geçiş gösteren jeneralize epileptik sendromları ise juvenil miyoklonik ve juvenil absans jeneralize tonik-klonik nöbetli epilepsilerdir. Parsiyel özellik gösteren tek gen kalıtımı ile gerçekleşen Yenidoğan ve Süt Çocuğu Epilepsileri, Selim Ailesel Neonatal, Selim Ailesel İnfantil Konvülzionlar ve Selim Ailesel Neonatal-İnfaltil Nöbetler başlıklarıyla 3 sınıfta toplanmaktadır. Otozomal dominant parsiyel epilepsiler ise Otozomal Dominant Noktürnal Frontal Lob, Ailesel Meziyal Temporal Lob, Ailesel Lateral Temporal Lob, Değişken Odaklı Ailesel Parsiyel Lob Epilepsisi başlıkları altında incelenmektedir. Farklı iyon kanallarında meydana gelen çeşitli mutasyonlar benzer fenotipler oluşturabilirken, aynı gen üzerinde meydana gelen belli bir mutasyon da farklı fenotiplere neden olabilir. Bu derleme epileptik sendromlara neden olan nöral kanalopatilerin genetik tabanı ve patofizyolojik etkileri üzerinden epilepsi sınıflandırmasına ait bir özet sunmaktadır.

Anahtar Sözcükler: Epilepsi, kanalopati, kalıtsal epilepsi, genetik mutasyon

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Inherited Epilepsy Syndromes

Introduction

Epilepsy describes a heterogeneous group of paroxysmal diseases thought to occur as a result of disturbances in neural networks. Around 50 million people around the world live with epilepsy. The estimated rate of patients with active epilepsy who still have seizures or need treatment is between 4 and 10 per 1000 people in the general population. This rate is between 7 and 14 per 1000 people in low-and middle-income countries. Globally, an estimated 2.4 million people are diagnosed as having epilepsy each year. In high-income countries, the incidence is between 30 and 50 per 100,000. In low-and middle-income countries, this figure has been recorded as double or higher. About 80% of people with epilepsy live in low-and middle-income countries. Epilepsy accounts for 0.6% of the global disease burden and leads to significant economic burden due to health care needs, early death and lost work productivity (1).

Studies show that the most common forms of idiopathic epilepsy in particular have inherited characteristics (2-6). Genes inherited by individuals from their families cause conformational mutations in ion channels. As a result of these mutations, unwanted neuronal firing occurs as a result of electrical potential changes in the cell and thus seizures are observed (1).

Ion channels play an important role in the creation and control of neuronal stimulation. With the discovery of mutations in genes that encode the formation of the ion channel, it has been shown that the issue is less or more stimulation of the affected tissues in various inherited neurological diseases. Ion channel disorders in other words, channelopathies are epilepsies in the idiopathic form, accounting for one-third of all epilepsies (7). Neuronal ion channels including voltage-gated channels (Na^+, K^+, Ca^{2+}, Cl^-) and ligand-gated channels (nicotinic ACh receptors, GABA receptors) have a role in the formation of hereditary epilepsies.

The genotype-phenotype relationship in epilepsy is quite complex. Different mutations in the same gene can cause phenotypes of various types (allelic heterogeneity), while mutations occurring in multiple different ion channels can cause similar phenotypes (locus heterogeneity). In addition, due to factors such as age and maturation of the brain, even the same mutation in the same gene can cause different phenotypes (2-6). These genetic changes and the epilepsies caused by them are given in Table 1.

Neuronal channelopathies were originally described based on genetic chain studies. Increased number of epileptic syndromes are usually included in neuronal channelopathies, and these canalopathies often begin at a certain age. The channelopathies include generalized epilepsies such as Genetic Epilepsy With Febrile Seizures Plus (GEFS+) associated with sodium channel and GABRG2 ($GABA_A$) receptor mutations (8). Also focal epilepsies such as BFNC associated with potassium channel mutations and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) associated with neuronal nicotinic receptor mutations are found in these channelopathies. Juvenile Myoclonic Epilepsy (JME) and Absans Epilepsy, which are forms of idiopathic generalized epilepsy, may be due to mutations in Ca^{2+} channels. Furthermore, mutations in Cl^- channel gene were found to be associated with certain types of epilepsies (9).

The aim of this study is to explain the types of hereditary epilepsies and the causes of these epilepsies. For this purpose, Mendelian and non-Mendelian idiopathic generalized epilepsy syndromes will be explained in the first part of the article. Then, partial epilepsies observed in newborn and children with single gene inheritance and partial epilepsies with automosomal dominant transition will be discussed. Later, types of epilepsy associated with paroxysmal dyskinesias, episodic ataxia and myokymia will be evaluated under the main heading of “channelopathies associated with epilepsies and other paroxymal neurological disorders”. Finally, we will focus on epilepsy genes that are not associated with the ion channel.

Generalized Epilepsy Sydromes

Mendelian Idiopathic Generalized Epilepsy Syndromes

Genetic Epilepsy With Febrile Seizures Plus (GEFS+)

GEFS+ was first described in 1997 by two scientists, Ingrid Scheffer and Samuel Berkovic (10). Febrile seizures (seizures occuring when body temperature is >38 °C) are the most common neurological disorder affecting 3% of children under 6 years of age Gardiner, M. In GEFS+, fever seizures often begin at age before 6 months and continue after 6 years of age with or without fever (11). The SCN1A, SCN2A, SCN1B and GABRG2 ion channel genes are thought to have a role in GEFS+ epilepsy (12). Mutations in these genes result in epilepsy syndromes belonging to the GEFS+ family showing autosomal dominant inheritance (13). As a result of mutations in these genes, epilepsy syndromes belonging to the GEFS + family that show autososomal dominant transition given in Table 2 (14). The most common phenotype is FS+; where febrile seizures (FS) continue after 6 years of age as tonic-clonic seizures without fever. Less common phenotype is myoclonic-astatic epilepsy syndrome with febrile seizures which is characterized by absance, myoclonic or atonic seizures (10,14,15).

The genetic heterogeneity of GEFS+ has been expressed in detail through loci. First locus (19q) was defined on the long arm of 19th chromosome (GEFS1) and corresponded to the gene encoding the sodium channel $\beta 1$ subunit (SCN1B). Second locus (2q) was defined on the long arm of 2nd chromosome (GEFS2) and corresponded to the gene encoding the sodium channel alpha subunit (SCN1A). To date, 9 different missense mutations have been reported in SCN1A. The missense mutation in the *SCN2A* gene, which encodes the sodium channel $\alpha 2$ subunit, is also localized on 2q and has been identified for the first time in a Japanese family (9). Voltage-gated sodium channels are essential in the production and propagation of the action potential in neuronal tissues. Biochemically, these channels consist of one large alpha subunit and 1 or 2 smaller beta subunits. The alpha subunit alone can show all the functional properties of the voltage-gated sodium channel, but requires beta subunits for normal inactivation kinetics. The mutations identified in sodium channel α and β subunits cause subtle changes in channel gating (increases in persistent sodium current, shifts in the voltage-dependence of steady state inactivation and/or resistance to frequency-dependent cumulative inactivation) which are thought to increase neuronal excitability and thus to predispose affected individuals to seizures (9,16).

Molecular studies have shown that gene mutations in the $GABA_A$ receptor subunit occur in GEFS+ syndromes and in the classic idiopathic generalized epilepsy family. In particular *GABRG2* gene mutations have been reported to be seen in GEFS+ and childhood absance epilepsy phenotypes. Mutations in the sodium channel subunit have been found mostly in GEFS+, but these mutations can also be seen in classical idiopathic generalized epilepsies (IJE) (13).

Autosomal Dominant Juvenile Myoclonic Epilepsy

JME is a type of seizure that occurs around puberty, characterized by bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks (MJ), observed mostly in the upper extremities. JME accounts for 5-10% of all epilepsies and 20-27% of IJE. The starting age of the JME often varies between the ages of 8-26 years, particularly 12-18 years (11,17). JME is often accompanied by generalized tonic-clonic seizures (JTKN) and less often by also absence seizures. Seizures can usually occur shortly after waking up or with sleep deprivation.

Table 1. Hereditary neurological diseases associated with neuronal ion channels

Disease	Channel protein	Responsible gene
Benign Familial Infantile Epilepsy	Nav2.1: Sodium channel, voltage-gated, type II, α subunit	SCN2A
Benign Familial Neonatal Epilepsy	Kv7.2: Potassium channel, voltage-gated, KQT-like sub-family, member 2	KCNQ2
	Kv7.3: Potassium channel, voltage-gated, KQT-like sub-family, member 3	KCNQ3
Childhood deficiency epilepsy	γ- Aminobutyric acid A receptor, α1 subunit	GABRA1
	γ- Aminobutyric acid A receptor, α6 subunit	GABRA6
	γ- Aminobutyric acid A receptor, β3 subunit	GABRB3
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2
	Cav3.2: Calcium channel, voltage-gated, T-type, α1H subunit	CACNA1H
Early infantile epileptic encephalopathy type 7	Kv7.2: Potassium channel, voltage-gated, KQT-like sub-family, member 2	KCNQ2
Early infantile epileptic encephalopathy type 11	Nav2.1: Sodium channel, voltage-gated, type II, α subunit	SCN2A
Early infantile epileptic encephalopathy type 13	Nav1.6: Sodium channel, voltage-gated, type VIII, α subunit	SCN8A
Early infantile epileptic encephalopathy type 14	KCa4.1: Potassium channel, sub-family T, member 1	KCNT1
Familial hemiplegic migraine type 3	Nav1.1: Sodium channel, voltage-gated, type I, α subunit	SCN1A
Generalized epilepsies with febrile seizures plus	Navβ1: Sodium channel, voltage-gated, type I, β subunit	SCN1B
	Nav1.1: Sodium channel, voltage-gated, type I, α subunit	SCN1A
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2
Juvenil myoclonic epilepsy	γ- Aminobutyric acid A receptor, α1 subunit	GABRA1
	Cavβ4: Calcium channel, voltage-gated, β4 subunit	CACNB4
Nocturnal frontal lobe epilepsy type 1	Cholinergic receptor, neuronal nicotinic, α4 subunit	CHRNA4
Nocturnal frontal lobe epilepsy type 3	Cholinergic receptor, neuronal nicotinic, β2 subunit	CHRNB2
Nocturnal frontal lobe epilepsy type 4	Cholinergic receptor, neuronal nicotinic, α2 subunit	CHRNA2
Nocturnal frontal lobe epilepsy type 5	KCa4.1: Potassium channel, sub-family T, member 1	KCNT1
Generalized epilepsy with paroxysmal dyskinesia	KCa1.1: Potassium channel, calcium-activated, wide conductivity, M family, α1 subunit	KCNMA1
Dravet syndrome	Nav1.1: Sodium channel, voltage-gated, type 1, α subunit	SCN1A
	γ- Aminobutyric acid A receptor, γ2 subunit	GABRG2

JME is a heterogeneous disease associated with several mutations. Major genetic loci thought to cause JME have been identified as epilepsy juvenile myoclonic 1 (EJM1), epilepsy juvenile myoclonic 2 (EJM2), and epilepsy juvenile myoclonic 3 (EJM3). A mutation in the GABRA1 gene on chromosome 5q34-q35 was identified in 14 members of a French-Canadian family with JME. In that family, the mode of inheritance of JME was autosomal dominant. The cause of seizures is the degradation of ligand-gated ion channels and the reduction of GABA. JME may also occur due to dysfunction in the β4 subunit of voltage-gated calcium channels as a result of mutation in the *CACNB4* gene on the 2q22-q23 locus (18). In addition, Cl^- channels have been affected as a result of a mutation in the *CLCN2* gene on locus 3q26 and JME has developed. It has therefore been determined that various channelopathies can lead to JME. In JME, maternal transition associated with EJM1 has also been shown. JME is transmitted five times more to children from mother than from father (19).

Epilepsy Associated With CLCN2 Gene Mutation

CLC-2, a chlorine channel found in the brain, is particularly found in neurons inhibited by GABA and has the role in providing the low intracellular Cl^- concentration required for the response of the inhibitory GABA (20,21). Disturbance of neuronal inhibitory system controlled by the inward current of Cl-can result in epilepsy. The *CLCN2* gene mutation encoding CLC-2 (voltage-gated Cl^- channel) has been found to be associated with IJE in three families. Two families were found to have inherited autosomal dominant patterns, and the third family had epilepsy in only one generation. The phenotype is very diverse, including patients with JME, absence epilepsies (childhood absence epilepsy and juvenile absence epilepsy) and isolated generalized tonic-clonic seizures (GTCS) (20,21).

Epilepsy Associated With Mutations in Calcium Channel Subunits

Mutations in CACNB4, the calcium channel ß4 subunit gene, have been identified in two small families with two affected individuals in each. In one of these families, the phenotypes overlapped with JME. In a small family with childhood absence epilepsy, another calcium channel subunit gene, CACNA1, was found to be mutated. Functional analysis of the mutation (R2162H) has shown that P/Q type CA++ channels have function gain by influencing G-protein modulation (22).

Non-Mendelian Idiopathic Generalized Epilepsies

It shows a complex inheritance of IJEs. In IJE, the original characteristic features of symptoms often overlap, and different IJE syndromes are collected in a single lineage. A locus identified on chromosome 18 is responsible for various IJE syndromes with adolescent onset including JME and juvenile epilepsy with absence and generalized tonic-clonic seizures (10). Analyses with polymorphism based on a single nucleotide have shown that the malic enzyme 2 haplotype increases the risk of IJE in homozygous cases. This enzyme is found in the neuronal synthesis of GABA. Blocking GABA synthesis facilitates the emergence of adolescent-onset IJE (12).

Fokal (Parsiyel) Epilepsies

Idiopathic Focal Epilepsies of Newborns and Infants Associated With Single Gene Inheritance

Benign Familial Neonatal Convulsions (BFNC)

Benign familial neonatal convulsions (BFNC) is a rare epileptic syndrome with dominant heredity characterized by frequent and short seizures that typically begin in the early days of life and disappear spontaneously after weeks or months. In very rare cases, adulthood epilepsy occurs (~10% of people). Although it has been recognized as generalized epilepsy in the ILAE classification in 1989, seizures have several clinical manifestations including tonic attacks, apnea, clonic, focal, and autonomic features (23). The majority of patients with BFNC have *KCNQ2* gene mutations on chromosome 20q13.3 and some of them have *KCNQ3* gene mutations on chromosome 8q24. In the nervous system, the products of the *KCNQ2* and *KCNQ3* gene combine to form potassium channels that produce M-current (24). M-current regulates neuronal excitability by reducing the tendency for repetitive firing. Neuronal M-currents are activators of other neurotransmitter receptor types but are inhibited by muscarinic acetylcholine agonists. Mutations in KCNQ2 or KCNQ3 decrease function in K^+ channels encoded by negative mechanism, consistent with autosomal dominant inheritance patterns of BFNC (16,25). Detailed examination of the KCNQ2/KCNQ3 complex, which contained one of the KCNQ2 mutations, showed that neonatal epilepsy was the result of mutation leading to changes in the K^+ channel gate and the M-current (26).

Benign Familial Infantil Convulsions (BFIC)

BFIC is an autosomal dominant disease seen in infancy. It is characterized by motor arrest along with short seizures and slow deviation of the head and eyes to one side. During the seizure, bruising, hypertonia and unilateral lip wobble are observed. Seizures begin at age of 3-12 months. Three locuses are responsible for the occurrence of this epilepsy. A mutation has been observed in 4 Italian families on chromosome 19q, in 7 French and Argentine families on chromosome 16p12-q12 (short arm of 16th chromosome) and on chromosome 2q24 in another 8 Italian families. No phenotypic differences have been observed between families with symptoms associated with mutations in these different chromosomes (27).

Benign Familial Neonatal-Infantil Convulsions (BFNIC)

Benign familial neonatal-infantil convulsions (BFNIC) syndrome is one of the autosomal dominant benign familial epilepsy syndromes seen in the first year of life. BFNIC syndrome begins in the range of 2 days to 7 months and shows symptoms that remain phenotypically between BFNC and BFIC. The mutation in the subunit gene SCN2A, which encodes the Na^+ channel, is the main cause of this disease and BFNIC have been found in 8 families until today (28).

Autosomal Dominant Partial Epilepsies

Genetic etiology is widely accepted in generalized epilepsies, but focal or partial epilepsies are mostly based on environmental factors such as birth accidents, trauma, infections, and brain lesions such as tumors and vascular damage. Despite this, there has been an increase in the diagnosis of families with dominant hereditary partial epilepsies over the past decade. Major familial focal epilepsies are ADNFLE, familial mesial temporal lobe epilepsy (FMTLE), familial lateral temporal lobe epilepsy (FLTLE), and familial partial epilepsy with variable foci (FPEVF) (29,30). So far, responsible genes have been identified only in ADNFLE (genes encoding ion channel subunits) and FLTLE (genes encoding non-ion channel subunits) (9,31).

ADNFLE is seen in almost every period from early childhood to adulthood, but most often starts around the age of 10 years. Almost all seizures occur in sleep. Mesial temporal lobe epilepsy was first described in 1994. A year later it was determined that the gene responsible for causing this epilepsy was on region 20q13.2. The gene CHRNA4 that encoded the neuronal nicotinic acetylcholine receptor (nACh-R) was then sequenced (this was also the first gene found in 1995). Another localization that causes this type of epilepsy has been found on the 15q region where different neuronal nicotinic acetylcholine receptor subunits exist. Mutations of α4 and β2 subunits of nicotinic acetyl choline receptor (CHRNA+ and CHRNB2) are the proven causes of ADNFLE (32).

Channelopathies Associated With Epilepsies or Other Paroxysmal Neurological Diseases

Epilepsies Associated With Paroxysmal Dyskinesias

Infantile convulsions and choreoathetosis (ICCA) syndrome is a syndrome associated with familial infantile convulsions that occur in association with paroxysmal choreoathetosis. Afebrile partial seizures occur between 3-12 months. Seizures begin with psychomotor arrests and deviation of the head and eyes, and sometimes become secondary generalised. Paroxysmal choreoathetosis begins in most patients between the ages of 5 and 9 years and tends to decrease in adulthood. A mutation on the 16p12-q12 locus has been observed to cause ICCA syndrome (33).

Generalized epilepsy and paroxysmal dyskinesia is a syndrome that accompanies generalized epilepsy, and paroxysmal dyskinesia is linked to chromosome 10q22. The mutation has been identified in the alpha subunit of the calcium-sensitive potassium channel. The mutant calcium-sensitive potassium channel has a noticeably larger macroscopic current. Single channel records show an increase in open-channel probability due to a 3-5-fold increase in Ca^{++} sensitivity. It has been suggested that increasing calcium-sensitive potassium channels in vivo would induce rapid repolarization of the action potential, leading to increased excitability, and would result in generalized epilepsy and paroxysmal dyskinesia, allowing these neurons to fire at a faster rate (34).

Epilepsies Associated With Episodic Ataxia

Another ion channel disorder with impaired excitability in the central nervous system is Episodic ataxia type 1 (EA-1) with myokymia. The disorder is mostly in the cerebellum. Patients complain of short kinesiogenic walking attacks, limb ataxia, or cerebellar dysarthria. In addition, partial epileptic seizures have also been reported in four families. Genetic analyses with EA-1 have indicated a link to chromosome 12p13. Mutations have also been found in the KCNA gene encoding the K^+ channel Kv1.1 (35).

Episodic ataxia type 2 (EA-2) with IJE: Mutations in the CACNB4 gene encoding the voltage-gated calcium channel on chromosome 2q22-23 cause IJEs and hereditary episodic ataxia (36). This gene encodes the β4 subunit of the protein that regulates the function of P/Q-type neuronal calcium channels. Voltage-gated calcium channels, especially P/Q-type channels, are important for neurotransmitter release in the central nervous system. The same gene has been also reported to be mutant in patients with sole IJE.

Absans epilepsy with episodic ataxia: A heterozygous mutation in the CACNA1A gene encoding the subunit of the P/Q type voltage-gated Ca^{+2} channel is the cause in individuals with complex phenotypes where absence epilepsy is associated with episodic ataxia (37).

Myokymia-Associated Epilepsies

BFNC that occur after myokymia have been described in two families. Muscular over-excitability resulted from the variable excitability of the lower motor neuron. Unlike other neurological diseases identified associated with epilepsy mentioned above, myokymia activity is continuous (38). Mutations in KCNNQ2 can cause typical BFNC and peripheral nerve stimulation that are not related to epilepsy, but also cause epilepsies of neonatal and early infancy with myokymia (39).

Non-Ion Channel Epilepsy Genes

Autosomal dominant partial epilepsy with auditory features (ADPEAF) is characterized by simple partial seizures with hallucinations or illusions, dream state, visual illusions, or speech disorders suggesting a lateral temporal source. If it spreads to the mesial temporal or extratemporal structures, it may develop into complex partial seizures (40). Magnetic resonance imaging results of patients are mostly normal. The onset time of the disease varies between youth and early adulthood. A genetic examination has shown a mutation in the LGI1 gene (leucine-rich glioma inactivated-1) on chromosome 10q24. This gene is involved in protein-protein interaction with ligand binding and in the development of the nervous system. LGI1 is the only gene responsible for temporal lobe epilepsy. This gene is also the only non-ion channel gene (40) that can be identified in idiopathic epilepsy. In some families with IJE (JME or lone GTCS), a second gene, EFHC1, which is not a direct ion channel gene, is mutant. This gene encodes a protein that interacts with R-type voltage-gated calcium channels and modulates these channels and has apoptotic activity. The third gene is the ATP1A2 Na^+, K^+-ATPase pump gene (41) on chromosome 1q23. This gene does not encode an ion channel but is involved in ion transport. This gene has been found to be a mutant in a family that includes patients with an idiopathic form of epilepsy and migraine (9).

Conclusion

In general, idiopathic epilepsies can be evaluated as ion channel pathologies (38,42). All mutations cause functional change. It is thought that channelopathies can reduce the transmembrane chloride gradient required for GABAergic inhibition, leading to membrane depolarization and hyperexcitability. There are many other diseases, episodic or non-episodic, caused by channel pathologies other than epilepsy. But channel pathologies are not the only cause of epilepsy. Non-ion channel genes, LGI1 and ARX, have emerged as major causes of specific epilepsy syndromes during the past years (26). As new genes are discovered and the functional consequences of disease-causing mutations are revealed, the genetic field of epilepsies will continue to evolve.

With genetic information from spontaneous mutant or genetically mutantized epilepsy animal models, or from epileptic humans, it has been understood that certain epilepsy syndromes are ion channel diseases. Idiopathic epilepsies are usually caused by mutations in genes that encode ion channels (9). Therefore, dysfunction in ion channels is associated with epilepsy. The complete elucidation of the functioning and genetic structure in ion channels will lead to the emergence of new approaches in the treatment of epilepsies mentioned above.

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