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Inherited epilepsies caused by defects in Na^+ channel genes and $(GABA)_A$ receptor genes

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Channelopathies are defined as inherited diseases, mostly located in an autosomal dominant gene. This review describes the significant number of new gene associated with genetic epilepsy syndromes that have emerged during the last decade, together with additional mutations relating to previously known gene associations. RECENT FINDINGS: Examples of ion channels most often associated with epilepsy are: A sodium channel, alpha1 subunit (SCN1A) defect was predominantly associated to generalized epilepsy with febrile seizures plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI). A mutation in GABA Receptor Gene, Gamma 2 subunit (GABRG2) is linked with childhood absence epilepsy with febrile seizures plus (FS+). Autosomal dominant form of juvenile myoclonic epilepsy was demonstrated to be a channelopathy associated with a mutation in GABA (A) receptor, alpha1 subunit (GABRA1). Additional effects of genetic variation, even within the same ion channel gene families, are likely to underlie the common idiopathic generalized epilepsies with complex inheritance. The genetic epilepsy is fast progressing toward a more detailed molecular dissection and definition of syndromes.

Keywords: *Inherited epilepsy, defective ion channel, Na^+ channel genes, $(GABA)_A$ receptor genes.*

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มัทนา อังศุไพศาล. Channelopathies ในแง่ของโรคชักแต่กำเนิดที่มีสาเหตุจากความผิดปกติของ Na⁺ channel ยีน และ (GABA)_A receptor ยีน. จุฬาลงกรณ์เวชสาร 2553 พ.ศ. - ม.ย.; 54(3): 195 - 204

Channelopathies คือ กลุ่มโรคที่ถ่ายทอดความผิดปกติทางพันธุกรรม โดยส่วนใหญ่่มักเป็นการถ่ายทอดลักษณะแฝงของยีนเด่น (autosomal dominant gene) บทความพิเศษนี้อธิบายถึงลักษณะผิดปกติของยีนในเชิงประสาทสรีรวิทยาในแง่การเปลี่ยนแปลงที่ผิดปกติของ ion channel ซึ่งถูกค้นพบใหม่ในช่วงราวสิบปีที่ผ่านมาว่ามีความเกี่ยวข้องกับสาเหตุการเกิดโรคชักที่เป็นมาแต่กำเนิด รวมถึงภาวะการเปลี่ยนแปลงที่ผิดปกติเพิ่มเติมของยีนตัวเดียวกันที่อาจส่งผลถึงโรคชักที่มีลักษณะแตกต่างกันด้วย โดยบทความนี้ได้เน้นอธิบายบางตัวอย่างของ ion channels ที่ค่อนข้างสัมพันธ์กับโรคชักแต่กำเนิดมากที่สุด ได้แก่ 1) ความผิดปกติของ Sodium (Na⁺) channel, alpha1 subunit (SCN1A) ที่สัมพันธ์กับกลุ่มอาการชักทั้งตัวจากไข้สูง (generalized epilepsy with febrile seizures plus - GEFS+) และยังสัมพันธ์กับกลุ่มอาการชักสะดุ้งอย่างรุนแรงในทารก (severe myoclonic epilepsy of infancy - SMEI), 2) ความผิดปกติของ GABA Receptor Gene, Gamma 2 subunit (GABRG2) ที่เป็นสาเหตุให้เกิดอาการชักเงิบหรือชักเหม่อร่วมกับการชักจากไข้สูงในเด็ก (childhood absence epilepsy with febrile seizures plus (FS+) และ 3) ความผิดปกติของ GABA (A) receptor, alpha1 subunit (GABRA1) ที่เป็นสาเหตุให้เกิดโรคลมชัก ที่พบในช่วงอายุวัยรุ่น ประมาณ 12 - 30 ปี (juvenile myoclonic epilepsy - JME) ในปัจจุบันการค้นพบสาเหตุของโรคชักที่ถ่ายทอดความผิดปกติทางพันธุกรรมมีความก้าวหน้ามาก สามารถอธิบายในเชิงลึกระดับ molecular basis ได้

คำสำคัญ : โรคชักแต่กำเนิด, ความผิดปกติของ ion channel, Na⁺ channel ยีน, (GABA)_A receptor ยีน.

Epilepsy is one of diagnostic reservoirs of neurogenetic disease (Table 1).⁽¹⁾ It affects up to 3% of the population and is manifest by recurrent seizures.⁽²⁾ Ion channels are important for neuronal excitability.⁽³⁾ Since 1995 many monogenic types of epilepsy have been linked to mutations in a number of different genes encoding either voltage-gated or ligand-gated channels.^(4,5) Importantly, the underlying genetic mechanisms involved seem to affect major pathophysiological pathways in the brain (Table 2).⁽⁶⁾ These genetic mutations not only lead to locus heterogeneity (the same clinical syndromes caused by mutations in different genes), but also to allelic heterogeneity (mutations in the same gene leading to changeable phenotypes).^(2, 7) As a result, the recognition that several monogenic epilepsy syndromes are channelopathies creates a new body of knowledge of molecular pathophysiology of seizure disorders.^(4, 5, 7) Examples of well published channelopathies related to idiopathic epilepsies include the defects of *Na⁺ channel genes* and *(GABA)_A receptor genes*. Hence, this review article focuses on the role of these defective ion channel genes in the molecular basis of epilepsy, based on locus and allelic heterogeneity.

Table 1. Diagnostic reservoirs of neurogenetic diseases.⁽¹⁾

Cerebral palsy
Mental retardation
Epilepsy
Movement disorders
Ataxias
Dementias
Atypical multiple sclerosis
Peripheral neuropathy

Background information of ion channels:

The ion channels are one of the integral membrane proteins mediating the transportation of selective ions into and out of cell membrane by the opening and closing states of gated pores.^(3,8) The ion channels responding to a change in membrane potential are called *voltage-gated ion channels*, while the other type influenced by chemical signals is *ligand-gated ion channels*. This review focuses on two ion channels which are *Na⁺ voltage-gated*, and *(GABA)_A receptor-ligand gated ion channels* that cause the genetic heterogeneity of epilepsies.^(3, 8)

Voltage-gated Na⁺ channels structure and function

(Figure 1):

Basically, *Na⁺ channels* present three important properties: their voltage-dependent activation regulated by depolarization, their inactivation after the rapidly transient activation within the depolarization phase, and gated-pore permeability that highly selects Na⁺ ions. The continuous process of opening and closing gate renders a macroscopic Na⁺ channel current. Then, when the *Na⁺ current* co-works with voltage-gated *K⁺ current*, they can produce action potential of the nerve cells.^(3, 8, 9) *Na⁺ channels* are mainly formed by a single (α) polypeptide chain that comprises of four repeating motifs, I-IV. Each motif consists of six membrane-spanning regions, S1-S6. The S4 region is the location of membrane potential detector called "the primary voltage sensor", whereas the pore-forming region is the loop between S5 and S6 domains. *Na⁺ channels* also contain one or more smaller β -subunit, formed by a single transmembrane domain with a short intracellular C

Table 2. Monogenic childhood epilepsies.⁽⁶⁾

Ion channel	Gene	Epilepsy syndrome	Brief name
K ⁺ channel	<i>KCNQ2</i>	Benign familial neonatal seizures	BFNS
	<i>KCNQ3</i>		
Na ⁺ channel	<i>SCN2A</i>	Benign familial neonatal infantile seizures	BFNIS
		Generalised epilepsy/febrile seizures+	
	<i>SCN1B</i>	Generalised epilepsy/febrile seizures+	GEFS+
	<i>SCN1A</i>	Severe myoclonic epilepsy of infancy	GEFS+ SMEI
GABA- receptor	<i>GABRG2</i>	Generalised epilepsy/febrile seizures+	
		Childhood absence epilepsy	GEFS+
	<i>GABRA1</i>	Childhood absence epilepsy	CAE
		Autosomal dominant juvenile myoclonic epilepsy	CAE ADJME
Cl ⁻ channel	<i>CLCN2</i>	Idiopathic generalised epilepsy	
		Autosomal dominant nocturnal frontal lobe epilepsy	IGE (JME)
Nicotinic acetylcholine receptor	<i>CHRNA4</i>		
	<i>CHRNA2</i>		
	<i>CHRNA2</i>	Autosomal dominant partial epilepsy with auditory features	ADNFLE ADPEAF
LGI1 (~K ⁺ channel)	<i>LGI1</i>		

terminus and a larger extracellular N terminus. β -subunit is responsible for improving Na⁺ current amplitude.^(3, 8, 9)

(GABA)_A receptor structure and function (Figure 2):

γ -aminobutyric acid (GABA) is one of the essential transmitters of synaptic inhibition in the brain and spinal cord. It binds to two main types of receptor: *type A and B GABA receptors*. The (GABA)_A receptors are ionotropic receptors associated with the influx of chloride (Cl⁻) ions of postsynaptic cells.

The opening state of these receptors leads to Cl⁻ influx into postsynaptic membrane. This results in increasing negative membrane potential, contributing to inhibitory process of the brain. Each (GABA)_A receptor requires two α -, two β -subunits and one γ -subunit to form a complete receptor. Despite the contents of different subunit types, each subunit resembles four transmembrane regions (TM1-TM4) and exhibits the pore-forming region, mostly made up of α -helices, at the TM2.^(2, 3, 8, 10)

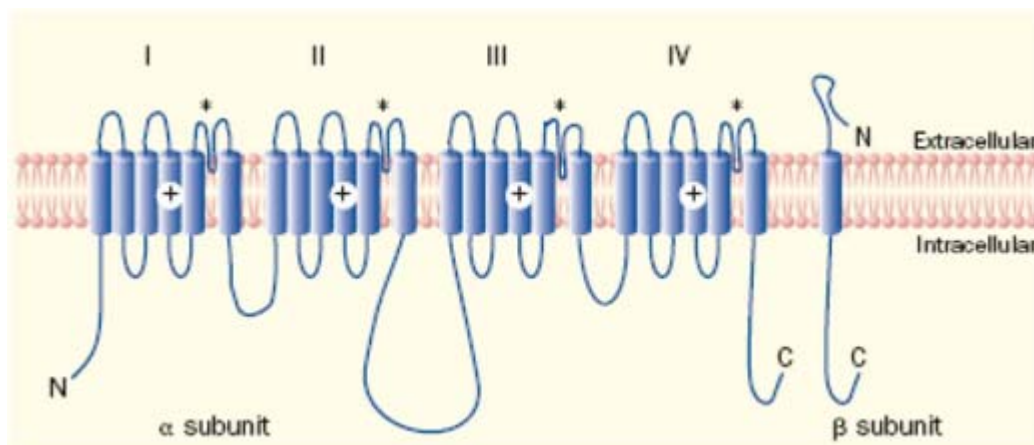


Figure 1. Na⁺ channel structure. The figure shows the structure of transmembrane of Na_v 1.4, the principal muscle sodium channel. The alpha subunit contains four homologous domains (I-IV), each of which consists of six helical transmembrane segments. The fourth segment of each domain (+) contains positively charged amino acids, which sense the transmembrane voltage. The loops between the fifth and the sixth segments (*) come together to line the central pore of the ion channel and determine its ionic selectivity. A beta subunit with a single transmembrane segment is associated with the alpha subunit.⁽⁷⁾

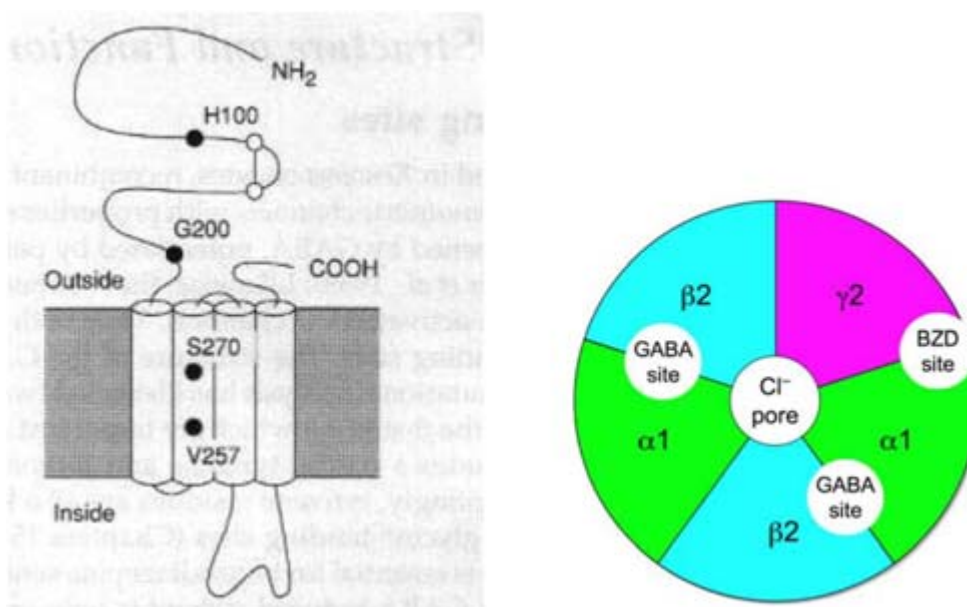


Figure 2.1 and 2.2. (GABA)_A receptor structure.

Figure 2.1: (GABA)_A subunit imbedded in a lipid bilayer (dark shading area). Each (GABA)_A receptor consists of two α -subunits, two β -subunits and one γ -subunit to form a complete receptor (figure 2.2). Each subunit resembles four transmembrane α -helixes regions (TM1-TM4) as depicted in cylinders in fig. 2.1. The second cylinder (the TM2) depicts the Cl⁻ pore-forming region. (8)

Genetic epilepsy and channelopathies:

How can channelopathies be inherited from one generation to another?

Channelopathies are defined as heritable diseases, mostly inherited in a dominant manner.⁽⁷⁾ Therefore, to understand how channelopathies are inherited from one generation to another; it is worth considering the genetics of the diseases. According to Ashcroft (2000), an autosomal dominant disease is referred to “the diseases that the phenotype is determined by the possession of a single mutant allele (the two copies of each gene) on the non-sex chromosome (an autosome)”.⁽⁸⁾ Hence, if a mother or a father holds an altered dominant gene, a child will risk to obtaining inherited gene as much as 50%. Although the majority of channelopathies are dominant inheritance, few can be identified as an autosomal recessive disorder, for instance, *glycine-receptor (ligand-gated)* mutations causing familial hyperekplexia which is the startle disease in infants.^(2,7) Ashcroft (2000) stated that the autosomal recessive disease is “one which only homozygotes who carry two mutant alleles are symptomatic”.⁽⁸⁾ Whereas, the carriers of the defected gene who are heterozygotes, having one normal allele and one altered allele, do not present symptoms but can pass their defective genes to their children. Perhaps both parents are heterozygotes, so in this case a child will have one-fourth chance to inherit the affected gene and exhibit the symptom.⁽⁸⁾ Finally, channelopathies can develop from various ways. Examples relevant to *Na⁺ channels* and *(GABA)_A receptor* mutations include mutations in the coding region and control region of an ion channel gene. Defects in the former region cause the gain or loss of channel function,

meanwhile the latter result in either under- or over-expression of channel protein.^(8, 11)

Mutations of *Na⁺ channels* and *(GABA)_A receptor*:

1. Generalized epilepsy with febrile seizures plus (GEFS+)

Perhaps, the most impressive locus heterogeneity of epileptic syndromes is febrile-afebrile seizures, occurring in many age groups.^(5, 7) Febrile seizures affect around 3% of children under six years of age, whilst febrile seizures plus (FS+) persist after six years or further develop to afebrile seizures. The latter has been termed generalized epilepsy with febrile seizures plus (GEFS+).^(12 - 16) Thus, the phenotypical spectrum of GEFS+ consists of, namely:

- febrile seizures
- febrile seizures plus (FS+)
- afebrile tonic-clonic seizures
- myoclonic, absence and atonic seizures or so-called complex partial seizures
- severe myoclonic epilepsy of infancy (SMEI).^(4, 7)

GEFS+ are resulted from the mutations of three voltage-gated *Na⁺ channel genes*^(2, 6, 9-16) and one ligand-gated channel gene, *(GABA)_A receptor*.⁽¹⁷⁾ All these defective genes are autosomal dominant inheritance.

1.1 GEFS+ related to *Na⁺ channel* mutations

Na⁺ channel gene mutations play a critical role in GEFS+. Mutations of three *Na⁺ channel* genes (*SCN1A*, *SCN2A* and *SCN1B*) have been linked with idiopathic epilepsy syndromes.^(2, 6, 9-16) Details of these three genes are as follows: *SCN1A* and *SCN2A* encoding α -subunits of *Na_v1.1*, and *Na_v1.2 channels* respectively^(16, 18, 19) and *SCN1B* coding for the auxiliary

Na⁺ channel β_1 -subunit.^(7, 14, 15) Meanwhile the neuronal Na⁺ channels Na_V1.1, and Na_V1.2 are responsible for the initial upstroke of neuronal action potentials, the accessory Na⁺ channel β_1 -subunit is necessary for Na⁺ channel fast inactivation.⁽⁷⁾ On the one hand, mutations in the pore-forming of SCN1A exhibit defects in fast inactivated gating, leading to a persistent Na⁺ influx as well as non-inactivating current after membrane depolarization.⁽¹³⁾ Therefore, the SCN1A mutations promote a gain-of-function in Na⁺ channel which in turn cause neuronal hyperexcitability.^(2, 7, 13) Similarly, a mutation in the pore-forming of β_1 -subunit gene, SCN1B, contributes to the loss of function of the β_1 -subunit that reduces the Na⁺ channel inactivation rate.^(2, 14) Thus, the alteration of SCN1A or SCN1B eventually results in similar effects. However, recent researches have reported that most mutations are discovered in SCN1A whereas SCN1B is the minority of GEFS+.^(2, 5, 9, 13-16, 19) Similarly, a study by Sugawara's group (2001) proposed that heritable defects in SCN2A can be found in some affected families.⁽¹⁸⁾

1.2 GEFS+ related to (GABA)_A Receptor γ_2 -subunit mutations

Although the main cause of GEFS+ is the mutations in SCN1A, mutations in type A GABA receptor genes can be associated with GEFS+ in certain families.^(6, 13, 17) The (GABA)_A receptors are ligand-gated Cl⁻ channels that mediate inhibitory neural activity. Despite a large gene family comprising of six major subunits that are: α , β , γ , δ , ϵ , and π , the (GABA)_A receptor predominately contains the limited combinations among three subunits: α , β and γ .^(7, 8) Evidence has been shown that the (GABA)_A receptor in the brain mostly consists of $\alpha_1 \beta_2 \gamma_2$ complexes.

Moreover, the γ_2 subunit is necessary for the localization of (GABA)_A receptors into inhibitory synapses.^(7, 8) Therefore, mutations in the GABA receptor gene, encoding the Gamma 2 (γ_2) subunit (GABRG2) are linked to childhood absence epilepsy with FS+.^(6, 17) Perhaps the common reason is that the γ_2 subunit dysfunction can cause a decrease in fast synaptic inhibition in the brain.^(7, 8) Thus, this effect leads to neuronal hyperexcitability as well as the final implications that occur from Na⁺ channel gene mutations.⁽⁷⁾ However, (GABA)_A receptor mutations remain a rare cause of epilepsy that have been identified in only a few families worldwide.^(2, 6)

2. Severe myoclonic epilepsy of infancy (SMEI):

2.1 SMEI related to Na⁺ channel (SCN1A) defect:

Interestingly, distinct mutations in SCN1A encoding α -subunits of Na_V1.1 often dominate in an uncommon convulsive disorder called severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome).^(2, 4-7, 20-22) This severely sporadic epilepsy is characterized by febrile and tonic-clonic seizures with onset during the first year after birth. Later on, the prognosis will be worsened by the developing intractable epilepsy, ataxia and globally delayed development. Currently, research evidence has been shown that more than 60 heterozygous SCN1A mutations, many of which are a genetic mutation that neither parent possessed nor transmitted, are causes of SMEI. Its mutations include missense, nonsense, and insertion/deletion alleles. Recent researches demonstrated that SMEI can be associated with both missense mutations and truncating mutations in the SCN1A gene. This defect contributes significantly to loss of function of the Na_V1.1 channel.^(2, 20, 21, 23) This

can be briefly explained that several mutations of *NaV1.1 channel* occur in the cytoplasmic linker between domains III and IV (Figure 1). These alterations consequently lead to channels continuing to flicker between open and shut states in the face of continued depolarization, and therefore contributing persistent sodium current. In a muscle fibre presenting mutant sodium channels, this persistent current is thought to impair repolarisation, and muscle fibres can therefore fire repeatedly, giving rise to myotonia. Therefore, an evidence suggests that SMEI is caused by loss-of-function mutations of the *SCN1A gene*.^(2, 4, 7) However, the reason why the altered *SCN1A gene* can generate both the common GEFS+ without mental delay and the SMEI with cognitive deficit is still unclear and needs further investigation.

3. Familial juvenile myoclonic epilepsy

3.1 (*GABA*)_A Receptor α_1 -subunits defect:

In addition to mutations in *GABRG2* resulting in GEFS+, the mutations in *GABRA1* which is the (*GABA*)_A receptor encoding α_1 -subunit, has been linked to an autosomal dominant form of juvenile myoclonic epilepsy (JME). JME is generalized epilepsy, making up at about 7% of adolescent and adult epileptic patients. Myoclonic jerks and mainly upper- limb involvement are the characteristics of JME.^(2, 23) These episodes tend to occur on awakening or following sleep deprivation. JME is the most frequent and, thus, one of the most important forms of inherited generalized epilepsy.^(2, 4, 23) The alteration of amino acid in the third transmembrane position (TM3) of the α_1 -*GABAR subunit* leads to the loss of function of GABA-mediated inhibitory neurons. This inadequate synaptic inhibition, therefore, causes an increase in neuronal excitability and account for the

seizures that defined JME.^(2, 4, 23) Nonetheless, whereas the *GABRG2* mutations exhibit the characteristics of febrile seizures (FS), the *GABRA1* mutations demonstrate myoclonic and generalized tonic-clonic seizures without any FS.^(2, 4, 6)

Conclusion

The defects of both *Na+ channels* and (*GABA*)_A receptor genes can cause genetically locus heterogeneity which is GEFS+. Moreover, all kinds of epilepsies caused by *Na+ channels* and (*GABA*)_A receptor genes mutations are autosomal dominant inheritance. Mutations in the different genes of the (*GABA*)_A receptor lead to distinct types of epilepsies, GEFS+ and JME, which occur in different age groups. *Na+ channel gene, SCNA1*, in contrast, can produce variable phenotypes of generalized epilepsies or the so-called allelic heterogeneity which are GEFS+ and SMEI with mental decline.⁽¹⁻⁸⁾ However, mutation, an alteration in a nucleotide, has a chance to develop at below 1% of the population,⁽⁶⁾ hereby; this implies that ion channel diseases rarely occur compared with the whole population. This does not necessarily mean that it should be ignored. By investigating the molecular basis of these rare monogenic epilepsy syndromes, ones can learn more about the importance of ion channel genes expressed in the brain.⁽²⁻⁸⁾ Certainly, The ultimate hope is that a mutation's finding will contribute to the therapeutic approach. For example, in SMEI, it was shown that some (Na-blocking) AEDs (anti-epileptic drugs) aggravate the seizures and should be avoided, while other ones are to be preferred.⁽²²⁾ The current knowledge also significantly benefits the diagnosis and advanced intervention program to relief the suffering of patients especially

children. For example, in January, 2009 the Miami Children's Brain Institute at Miami Children's Hospital, USA⁽²⁴⁾ created Ion Channel Epilepsy Program to standardize and improve the quality of clinical care provided to children with epilepsy caused by ion channel mutations.

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