J Med Sci 2009;29(4):167-172
http://jms.ndmctsgh.edu.tw/2904167.pdf

Current Proceedings of Febrile Seizures and Related Epileptic Syndromes in SCN1A: from Bedside to Bench

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Febrile seizures (FS) characterize the majority of childhood seizures, it is well recognized highly inheritance in family of children with FS. Several genetic loci related to FS had been defined imply the genetic heterogeneity of FS. Nevertheless, molecular genetic approaches toward understanding FS related epilepsies have been explored this decade; especially sodium channel mutation 1α (*SCN1A*). Among them, generalized epilepsy with FS plus (GEFS+) and severe myoclonic epilepsy of infancy (SMEI) are highlighted. This review demonstrates recent development from clinics to genetics of FS and the update of genetics in FS associated epilepsy in *SCN1A* mutation and related epileptic syndromes.

Key words: febrile seizures, sodium channel, epileptic syndrome.

DEFINITION ANDEPIDEMIOLOGY OF FEBRILE SEIZURES (FS)

Febrile seizure (FS) is a common disorder of children, generally involved 2-5% of children, and the prevalence is 3.2% in Taiwan[1]. However a higher affect rate of FS is 6-9% in Japan[2,3]. The definition of FS from International League Against Epilepsy (ILAE) is that seizures associated with a febrile illness in the absence of central nervous system (CNS) infection or acute electrolyte imbalance in children >1month of age without pervious afebrile seizures[4]. Ordinarily, FS has a favorable outcome and is almost known only rare consequence into epilepsy except children of FS concurrent with afebrile seizure[5]. Also, Annegers et al. report the high consequence to partial seizures in complex febrile seizures than in simple febrile seizures[6].

Ordinarily, FS is provoked by fever within range 6 months and 6 years old, and half cases of FS happen at the age from 1 to 2 1/2 years old, statistically the peak age of FS is 18 months old. The incidence of FS is slightly higher in male than in female. Near 90% of children with FS, the duration of FS is less than 10 minutes, and about 10% is over fifteen minutes. Nevertheless, five percent of FS develop febrile status epilepticus. The clinical outline is summarized in table 1.

Table 1

Gender (M:F)	Male 1.4	Female:1
Age(mean: 18m)	6m-6yr	50% on 12-30 m
Family history	FS in 24%	Epilepsy in 4%
FS duration	87%:<10min	9%:>15min

Hauser et al. had traced that the increased risk for FS in siblings, offspring, and nieces and nephews of probands[7], implying that FS is a highly related genetic disorder. About one fourth of FS can be traced positive family history of FS. On the other hand, only 4% of FS have epileptic family. Thus, increased occurrence of FS is abstracted in table 2.

Table 2 Risk factors for development of the first FS

First or 2nd-degree relative with a history of FS
Siblings had FS
History of FS in both parents: 40-80%
History of FS in a parent: 20-30%
No history of FS in the parents: 5-20%
Neonatal nursery stay >30 d
Attendance at daycare
Developmental delays

Received: February 4, 2009; Revised: February 25, 2009; Accepted: February 26, 2009
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CLINICAL MANIFESTATION IN FS

The classic clinical manifestations of simple FS present as generalized seizure, duration less than fifteen minutes, without recurrence within 24 hours; alternatively is defined as complex FS. Statistically, 9 to 35% of FS is attributed to complex FS (table 3).

Table 3 Clinical classification of FS

Simple (65-91%)	Complex (9-35%)
Generalized seizures	Partial seizures
<15min	Prolonged >15min
Do not recur within 24 h	Recur within 24 h
No previous neurologic problems	Known neurologic problems of the patient

Adapted and modified from reference[8] Generally, the recurrence of FS is variable from quarter to half and overall the average of recurrent FS is around 30% (variant from 25 to 50%). Additionally, 70% of FS occurs within 1 year old and 90% less than 2 years old. However, only 9% of FS has three times and more of recurrent FS. Tracing these cases of recurrent FS, some associated factors are list in table 4.

Table 4 Risk Factors for FS recurrence

1. Family history of FS (50%)
2. <Age18 mo (50%)
3. Lower peak fever with prior FS
4. Shorter duration<1 hr of fever before FS

Either age less than 18 month or positive family history of FS has increased recurrent rate of FS up to 50% respectively. In addition, when child having minor fever less than 38.5℃ prior FS and disclosing shorten duration less than one hour of fever, both have relevance to increase recurrent rate of FS[9].

The associated factors of FS subsequently evolving into epilepsy are attributed as (a) neurological abnormalities or psychomotor retardation, (b) family history of epilepsy and (c) complex FS. If the patient had none of three main risk factors, the incidence of consequent epilepsy is about 1% similarly to general populations. However, the occurrence of epilepsy is increased to 2% when the patient has one added risk factor, and up to 10% in patient of FS has two or more main risk factors. Nevertheless, when children with FS are full of whole factors including neurologic abnormalities and family history of epilepsy as well as all items of complex FS, more than 50% of them have consequence of epilepsy. Recently, Nakayama et al. review that there are Six susceptibility FS loci recognized on chromosomes 8q13–q21 (*FEB1*), 19p (*FEB2*), 2q23–q24 (*FEB3*), 5q14–q15 (*FEB4*), 6q22–q24 (*FEB5*), and 18p11 (*FEB6*). Moreover, mutations in the voltage-gated sodium channel α-1, α-2 and β-1 subunit genes (*SCN1A*, *SCN2A* and *SCN1B*) and the GABAA receptor α-2 subunit gene (*GABRG2*) have been identified in families with a clinical subset of seizures termed "generalized epilepsy with febrile seizure plus (GEFS+)"[10]. To our interest, variant mutations of SCN1A are linked to GEFS+ and severe myoclonic epilepsy of infancy (SMEI) – an epileptic syndrome with grave prognosis respectively.

VOLTAGE-GATED SODIUM CHANNEL AND SCN1 GENE

Voltage-gated sodium channels (Na_v) play a role of cellular excitability[11], Na_v provides a delicate sensing mechanism to equilibrium membrane-potential, these channels respond to minor voltage declinations by opening their gates to allow Na^+ pouring into the cells. Over the last decade, these so-called Nav channelopathies are encoded in several electric excitable disorders, chiefly focus on cardiac arrhythmia and epilepsy.[11-13]. Considering Na_v channelopathy in neuron, these neurons spontaneously enter periods of simultaneous firing leading to recurrent seizures and/or brain dysfunction. Moreover, epileitiologists highly aware in the epilepsy field for a peculiarly association between febrile seizures and Na_v[14,15]. Three sodium channel genes, including SCN1A, SCN2A and SCN3A, are clustered on chromosome 2q24 that are encoded as α subunit of sodium channel forming a pore[16] (figure 1). The isoform in $Na_v1.1$ (gene symbol *SCN1A*) is highly expressed in CNS and produces variant phenotypes of seizure and epilepsy ranging from benign to extremely severe had been uncovered progressively[17-20]. A total 6,030-bp of SCN1A mRNA is organized into 26 exons spanning about 100 kb of genomic sequence. Alternative splicing of SCN1A results in two isoforms that differ by 33 bases in the 30 end of exon 11, resulting in an 11 amino acid difference between the translated proteins[21] forming four domains, each contains six transmembrane segments (figure 2).

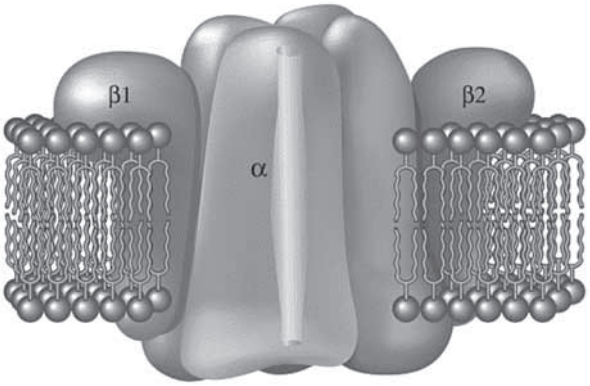

Fig. 1 Structure of neuronal voltage-gated Na^+-channel. Neuronal voltage-gated Na^+-channel, the major generator of action potentials in neurons, is assemble of three subunits; an α subunit and two auxiliary β subunits, β1 and β2. This α subunit preserves a large pore forming molecule and sufficient to function as a Na+-channel on its own. Both β1 and β2 subunits regulate channel function providing inactivation kinetics to Na^+-channel. The β1 subunit binds to the α subunit by a non-covalent linkage, while β2 subunit binds to the α subunit by a disulfide bond covalent linkage. There are several subtypes of α subunits expressed in the central nervous system: α1, α2 and α3 form electrophysiologically different Na^+-channels; $Na_v1.1$, $Na_v1.2$ and $Na_v1.3$, respectively. They have developmentally and spatially different expression patterns and $Na_v1.2$ is the most abundant in adult brain.[46]

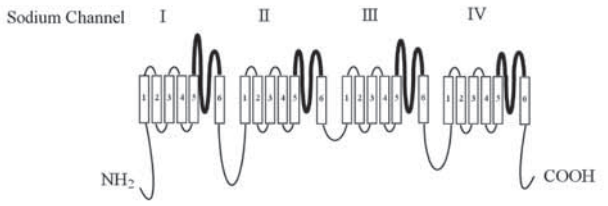

Fig. 2 Schematic representation ofthe SCN1A protein consists of four domains designated I~IV, each contains six transmembrane segments designated S1~S6.

TWO COMMON EPILEPTIC SYNDROME TYPE ENCODED WITH VARIANT MUTATION OF SCN1

GENES: GEFS+ and SMEI

Since Scheffer and Berkovic first nominate GEFS+ [MIM 604236] defined as a genetic disorder. Clinically, these children with GEFS+ usually manifest of febrile seizures extending beyond 6 years, with or without associated *afebrile* generalized tonic–clonic seizures (GTCS), lacking other recognized syndromes and consequently benign outcome[22]. Afterward, GEFS+ is approved as a common epilepsy syndrome at present [15,16,23-25]. Instead, (SMEI) (MIM# 607208) - a devastating epileptic syndrome had been discovered to be related with both febrile seizure and SCN1A mutations; but almost poor outcome eventually. Since 1978, Dravet first postulated SMEI, which is recruited as an epileptic syndrome in the ILAE classification, proposed by the Commission on Classification and Terminology of the ILAE (1989)[4]. The diagnosis of SMEI is based upon several clinical features including: (a) appearance of seizures, typically generalized tonic–clonic, during the first year of life; (b) impaired psychomotor development following onset of seizures; (c) occurrence of myoclonic seizures; (d) ataxia; and (e) poor response to AEDs. Otherwise, borderline SMEI (SMEB) and intractable childhood epilepsy with generalized tonic-clonic seizures (ICEGTC) have been attributed to patients with an epilepsy syndrome close to SMEI but in whom myoclonic seizures are absent and less severe psychomotor impairment is manifested[26-28]. Otherwise, a number of epilepsy syndromes are related with SCN1A gene (MIM# 182389) mutations, apart from typical SMEI, SMEB, ICEGTC, and GEFS+ (MIM# 604233) were summarized in Table 5[29-32].

Table 5 Common types of febrile seizure related epilepsy encoded with abnormality of SCN1 genes

Disorder	Chromosome	Genes (product)	Reference
GEFS+1	19q13.1	SCN1B (Na+-channel)	33, 34
GEFS+2	2q24	SCN1A (Na+-channel)	30, 35, 36
ICEGTC	2q24	SCN1A (Na+-channel)	27, 37
SMEI	2q24	SCN1A (Na+-channel)	35, 37, 38
Borderline SMEI	2q24	SCN1A (Na+-channel)	35, 39

PREVALENCE

Statistically, SMEI and its derivatives including SMEB, ICEGTC etc is undoubtedly the most common (86.1%) phenotype encountered with *SCN1A* mutations. Second most, but uncommon (6.7%), are GEFS+ and FS related syndromes. The remaining association with syndromic epilepsies encompass cryptogenic focal and cryptogenic generalized epilepsy (about 3%), and

sporadic occurrences of myoclonic astatic epilepsy severe idiopathic generalized epilepsy of infancy (0.8%), and merely 0.3% of severe idiopathic generalized epilepsy of infancy, Rasmussen's encephalitis, infantile spasms and Lennox-Gastaut syndrome respectively[15,40,41].

DILEMMA OF PHENOTYPE AND GENOTYPE BETWEEN GEFS+ AND SMEI

A total of some 330+ genetic alterations of SCN1A was reviewed recently[42], however it is extremely difficult to validate a faithful correlation between the reported phenotypes and genotypes. Presently, it has become widespread practice in the clinic to perform candidate genetic screenings mutations in SCN1A for the strong links to either SMEI or GEFS+. Studies showing a higher concordance rate in monozygotic rather than in dizygotic twins also support a genetic contribution[43,44]. But, one quandary is that whole genomic sequence of *SCN1A* cover more than 81 kb causes an infeasible work for regularly complete delineation of sequence. For example, one copy of *SCN1A* missing as a result of a genomic deletion cannot be detected in that fashion. Similarly, microchrosomal deflection were reveled in SMEI, that cannot be detected from conventional sequence methods[38]. However, intact SCN1A is displayed in some patients of GEFS+/SMEI[17,45]. Nevertheless, a number of studies with partial success genomic alterations extending beyond short insertions, deletions, or point mutations commonly produce negatives in analyses where exonic sequencing is employed. And the other challenge is that it is impossible as the *SCN1A* regulatory regions are not well established[20].

SUMMARY

We address from the clinical inspection of a common childhood neurologic disorder - febrile seizure to the genetic currency of related epileptic syndromes. The enormous diversity is arised in between simple febrile seizure – a benign neurologic disorder and SMEI - a devastating neuronal disorder. Finally, we conduct febrile related epileptic syndromes attributed to neuronal channelopathy of the *SCN1A* mutations chiefly. We hope this review to provide a close link of basic and clinical proceeding from bedside to bench.

ACKNOWLEDGEMENTS

We are indebted to our patients with epilepsy and their families for their encouragement to complete this review. This work was supported by the Cheng-Han education Foundation.

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