The sodium channel α1 subunit (SCN1A)-related epileptic phenotypes

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Abstract
Voltage-gated sodium channels (Nav) are neuronal channel proteins responsible for action potential initiation. Any alteration of the kinetics that determine the gating of these channels can have impact on cellular excitability. Abnormal Nav1.1, one of the five isoforms present in the nervous system, and encoded by the sodium channel α1 subunit (SCN1A) gene, has been associated with a wide spectrum of epileptic phenotypes clinically ranging from extremely benign to very severe forms. Most of these forms share febrile seizures as main or presenting seizures type. In this review the authors summarize the SCN1A-related epileptic phenotypes discovered to date together with the main underlying genetic mechanisms.

Keywords: voltage-gated sodium channel, SCN1A, Nav1.1, epilepsy, phenotypes

Introduction
Monogenic epilepsies and epileptic encephalopathies represent an increasing number of disorders linked to mutations epilepsy-causing genes. In the majority of cases, mutations involve genes coding for ion-channel proteins, although anomalies of non-ion-channel proteins have been coupled with monogenic epilepsy (1). Genotype–phenotype correlations have not been completely elucidated, since undefined genetic and environmental factors are likely to play a role in determining the phenotype. In the last twenty years most of researchers’ studies have been focused on neuronal ionic channels, as well as the family of voltage-gated sodium channels (Nav) . Among these, the isoform 1.1α encoded by the sodium channel α1 subunit (SCN1A) gene, is now known as one of the main protein that can be altered in epileptic disorders. The SCN1A-related epilepsies can usually be classified as GEFS+ (Genetic Epilepsy with Febrile Seizures Plus). Some other phenotypes may present a wide range of clinical manifestations, from mild to severe forms (2).

Voltage-gated sodium channels and the Sodium Channel α1 subunit
Voltage-gated sodium channels are neuronal channel proteins sensitive to minute voltage reductions and act with a positive feedback loop by opening their gates and allowing Na+ to rush into the cells, thus being responsible for action potential initiation. Voltage-gated sodium channels are structured in four homologous domains (D1–D4) that comprise six transmembrane regions each (S1–S6). Positively charged residues located in the S4 transmembrane region act as sensing mechanism and register changes in the cytosolic membrane-potential. Nav function is regulated by β subunits, smaller than α subunit, that determine the sub-cellular location of the Nav channel complex modulate the current (2). Five voltage-gated sodium channel isotypes exist in the nervous system: Nav1.1, Nav1.2 Nav1.3, Nav1.6, Nav1.7. All the isoforms are expressed in the brain, with the exception of Nav1.7, that is mainly expressed in peripheral neurons. Nav1.1 is encoded by SCN1A, an 81-kb gene of 26 exons located at 2p24.3, that generates a protein incorporating between 1967 and 2009 amino acids (2). Differences in Nav1.1 length depends on splicing variability. Any alteration of the kinetics that determine the gating of these channels can have impact on cellular excitability. On the basis of the spatial and temporal expression pattern of the Nav channel both, gain- and loss-of-function, are a possible cause for an excitatory imbalance. Anomalies in Nav1.1, together with the so-called Nav channelopathies – have been coupled with various pathologies of heart (i.e. Nav1.5 defects in Brugada syndrome or in type III long QT syndrome), muscle (i.e. Nav1.4 anomalies in congenital myopathy or hyperkalemic periodic paralysis), and brain (i.e. Nav1.1 dysfunction in various epilepsy types, as discussed in this paper) (3). In the context of epilepsy, Nav1.1 is the sodium channel whose abnormalities have been most implied in seizure disorders. Similarly, also anomalies of β subunits have been associated with various phenotypes of epilepsy (3). Most of these forms are linked to gain-of-function anomalies of the Nav 1.1 subunit (SCN1A) gene, and its variant (Borderline Severe Myoclonic Epilepsy of Infancy and Intractable Childhood Epilepsy with Generalised Tonic–Clonic Seizures). Genetic epilepsy with febrile seizures plus (GEFS+) (OMIM #600233) is a familial, autosomal dominant epileptic syndrome with a large pattern of intra-familial and extra-familial phenotypic variability. Patients with GEFS+ may suffer from febrile seizures (FS) after the 6th year of age (called febrile seizures plus [FS+]) and atypical absence seizures (SMEI) (9). SMEI children who have inherited mutations from asymptomatic or slightly affected parents) (10). In a recent study, it has been reported that diphtheria–tetanus–pertussis vaccination might trigger the earlier onset of DS in children who, as in all previously reported families, are destined to develop the disease, without influencing other clinical aspects (e.g., intellectual outcome and subsequent seizure type) (11). Regarding genetic factors, studies on the mouse model for GEFS+ carrying SCN1A mutations have shown that voltage-gated ion channel variants in Sodium channel α2 and β subunits (SCN2A, SCN8A), and potassium channel (KCNQ2) can modify the phenotype (modifying genes), influencing clinical presentation and severity (18, 19). Several authors have reported mutations in SCN1A in the form of mosaicism as an important cause of familial atypical epilepsy (e.g., SMEI children who have inherited mutations from asymptomatic or slightly affected parents). In a recent study, mosaicism was found in 7% of the families with DS (20).

The hypothesis is suggested that the SCN1A gene is dosage-sensitive and has a critical threshold with a phenotype depending on the percentage of functional sodium channels: in case of haploinsufficiency (<50% functional Na+ channel reduction) SMEI is observed; in case of mosaicism (<50% functional Na+ channel reduction), milder phenotypes are reported. However, these observations are derived from blood lymphocytes and not from neurons (21-24). Mosaic missense SCN1A mutation has been found in families with GEFS+ (25), two families the children who inherited the mutation did not develop SMEI, as in all previously reported families, but a less severe phenotype consisting in GEFS+ (25). Finally, a twin study showed that de novo mutations in SCN1A may occur at any time, from the premonula stage of the embryo (causing disease in the subject) to adulthood

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various conditions, myoclonic, and hypotonia, harbored SCN1A mutation. These patients exhibited seizures onset between 4.5 and 7 months, atonic and hemiclonic seizures), EEG showed multifocal epileptic activity without generalized or bilaterally synchronous discharges. Mild atrophy was noticed in two cases at brain MRI. The mutation were de novo in two cases and inherited from the mother in one case.

The term Severe Infantile Multifocal Epilepsy (SIMFE) has been used by Harkin and colleagues reported in 2007 six SCN1A mutations in twenty-five children with MMPSI which had been screened for mutations of the main candidates genes [e.g. KCNQ2 and 3, CLCN2 revealed no mutations in three patients with MMPSI (26). No underlying organic substrates have been identified in children with MMPSI, and a later onset of cognitive regression. It is of interest that clinical features of SIMFE is similar to that of the severe epilepsy with multiple independent spike foci, an epileptic phenotype related to various conditions, as tuberous sclerosis or birth asphyxia. Differently, the term SFME has been used for children with epileptic encephalopathy of unknown origin and SCN1A mutations.

In the same study, a further patient with CFE was discovered to have a de novo SCN1A mutation; this patient presented recurrent episodes of status epilepticus starting from the 18th month of life, normal development and no other neurological signs (11). All these four mutations were discovered in a group of 18 cases of CFE (22%).

The other four patients had different patterns with variable seizures onset and semiology, developmental delay (from normal to severe intellectual disability), and neurological signs (hemiparesis, ataxia, hypotonia, intermittent movement disorder) (11). SCN1A anomalies have been reported also in few patients with Myoclonic-Astastic Epilepsy (or Doose syndrome) (11) and with Lennox-Gastaut syndrome (11, 31). Finally, a mutation of SCN1A gene has been identified in a child with West syndrome, although this remain the only reported case to date (32).

Conclusion SCN1A-related seizure disorders encompasses a spectrum that ranges from mild phenotypes as FS or GEFS+ to more severe or devastating forms as SMEI, SFME, MMPSI, MAE, ICE-GTC, and SMEB. The phenotype of SCN1A-related seizure disorders can vary even within the same family due to genetic and environmental factors, most of them are still unclear. This group of seizure disorders is inherited with an autosomal dominant fashion. A patient with mutation in SCN1A may have an inherited or de novo mutation, and has a 50% chance of transmitting the anomaly to the offspring. The risk of developing the phenotype is less than 100% because of reduced penetrance. Inherited mutations have been more frequently identified in mild phenotypes, while de novo anomalies usually are responsible for severe forms.

The diagnosis of these epilepsy syndromes can be reached with sequence analysis and deletion testing of the SCN1A gene, having clinical, MRI and EEG follow-up.

Table 1: Clinical, MRI and EEG summary of the main SCN1A-related phenotypes. List of abbreviations: FS Febrile Seizures, FS+ FS plus, FSE Febrile Status Epilepticus, GTCS Generalized Tonic-Clonic Seizures, HS Hot Water Seizures, Absence Seizure, A Altonic Seizures, P Partial Seizures, Tonic-Clonic, Tonic, M Myoclonic Seizures, Hemiclonic Seizures, IS Infantile Spasms, AA Atypical Absence, mo months, y years, d day, PM Psycho-Motor, F Focal, G Generalized, SW Spike-waves

References


