

Mutations of Ion Channels in Genetic Epilepsies

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Abstract Epileptogenic mutations have been identified in several ion channel genes, leading to the concept that several epilepsies can be considered channelopathies. However, increasing number of genes involved in a diversity of functional and developmental processes are being recognized through whole exome or genome sequencing, confirming that there is remarkable complexity underlying epileptogenesis. Additionally, recent studies of large cohorts of patients suggest that many patient-specific mutations in several genes are important for generating a particular phenotype, rather than mutations in a few genes common to most of the patients.

We will review the epilepsy syndromes linked to ion channel gene mutations and the main results of genetic and functional studies, highlighting that also other genes can be important but stressing the central role of ion channels in the pathophysiology of genetic epilepsies. Although the picture is becoming more complex than previously thought, the identification of epileptogenic mutations in patients before epilepsy onset and the possibility to develop therapeutic strategies tested in experimental models may facilitate experimental approaches that prevent epilepsy or decrease its severity.

Because neuronal excitability depends on the activity of voltage-dependent or receptor-activated membrane ion channels, their dysfunctions have been hypothesized to have a central role in epilepsy. In fact, early observations have shown that epileptiform neuronal activity can be induced by spontaneous or experimental modifications of the properties of ion channels leading to alterations of neuronal excitability or synaptic transmission (McCormick and Contreras 2001; Avanzini and Franceschetti 2003).

However, the first demonstration that a human disorder of excitability is caused by a genetic mutation of an ion channel came from the identification of a $\text{Na}_v 1.4$ Na^+ channel α subunit mutant (gene *SCN4A*), causing a skeletal muscle disease: hyperkalemic periodic paralysis (Ptacek et al. 1991). Since then, mutations of ion

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channels have been identified in several diseases whose pathological mechanism involves defects of cellular excitability, the “channelopathies” (Ptacek 1997), including hemiplegic migraine, episodic ataxias, myotonias, hyperekplexia and cardiac syndromes (Kass 2005; Ashcroft 2006; Kullmann 2010). These diseases, similarly to idiopathic epilepsies, show acute and transient presentation of symptoms in individuals that otherwise appear normal. Indeed, few years after the discovery of hyperkalemic periodic paralysis mutations, the first epileptogenic mutation of an ion channel was identified in the $\alpha 4$ subunit of the neuronal acetylcholine receptor of patients affected by autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (Steinlein et al. 1995). Since then numerous other mutations and genetic variants of ion channel genes have been identified in different forms of epilepsy (Fig. 1; Avanzini et al. 2007; Helbig et al. 2008; Reid et al. 2009; Kullmann 2010; Mantegazza et al. 2010b; Guerrini et al. 2014), but the picture is becoming less clear than it was foreseen.

Several genes that do not codify for ion channels and sometimes have still unidentified functions have been implicated in genetic epilepsy. Moreover, phenotypic variability is often large, making more difficult the correlation between mutations in specific genes and specific epileptic syndromes, and complicating early diagnosis and genetic counseling. Phenotypic variability has been ascribed to genetic modifiers: polymorphisms or other genetic variants that can modulate the effect of the mutation. Notably, mutations are defined as modifications in the sequence of a gene that are clearly identified as the cause of the disease, thus the term should be used for mendelian monogenic disorders. Genetic variants are instead modifications that contribute to disease susceptibility, and their implication in disease is often inferred from the fact that the variants are mainly found in patients and that they induce functional effects. In polygenic epilepsies, a specific epilepsy phenotype can be generated by the combination of less penetrant alleles with large effect and of polygenic alleles with small effect. Novel technologies have allowed the sequencing of whole genomes (whole genome sequencing, WGS) or of their coding part (whole exome sequencing, WES), identifying an increasing number of genetic variants. However, the identification of their importance for determining a specific phenotype is not straightforward. Moreover, in many cases both genetic and acquired factors can contribute to the determinism of epilepsy, and environmental factors can have an important role in determining phenotypes also in forms with Mendelian pattern of inheritance (Berkovic et al. 2006).

However, despite these complications, several studies have indisputably linked ion channels to specific epileptic syndromes and pathogenic mechanisms.

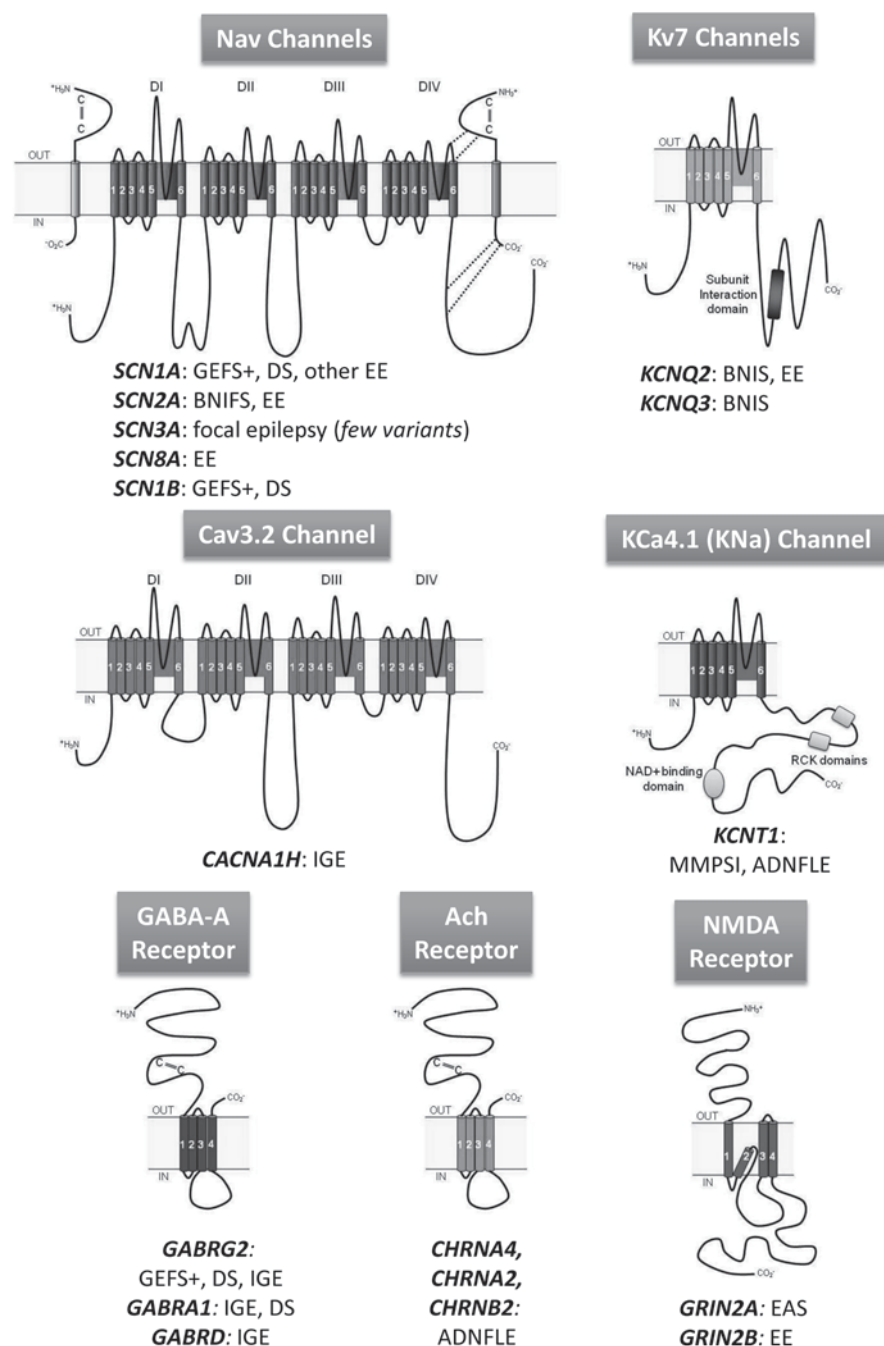


Fig. 1 Basic structure of main voltage- and ligand-gated ion channel proteins involved in genetic epilepsy. The structure of the subunits targeted by mutations/variants identified in genetic forms of epilepsy are shown. The names of the genes and the forms of epilepsy in which they are involved

Voltage-gated Na⁺ Channel SCN1A Gene-related Epilepsies and Epileptic Encephalopathies: A Prototypical Spectrum of Severity

Voltage gated Na⁺ channels (Na_v) are essential for the generation of cellular excitability, target of antiepileptic drugs and their mutations are important causes of genetic epilepsy (Mantegazza et al. 2010a; Marini and Mantegazza 2010; Catterall 2012). Na_v are composed by a principal pore-forming α subunit (nine isoforms: Na_v1.1–Na_v1.9 for the proteins, SCN1A–SCN11A for the genes), and by auxiliary β subunits (four isoforms: β 1– β 4 for the proteins, SCN1B–SCN4B for the genes) (Mantegazza and Catterall 2012). The primary sequence of α subunits contains four homologous domains (DI–DIV), each comprising six predicted transmembrane segments (S1–S6) that form voltage-sensing modules (S1–S4; S4 is the voltage sensor) and pore modules (S5–S6) in each domain. The β subunits contain a single transmembrane segment.

SCN1A/Na_v1.1 is one of the most clinically relevant epilepsy genes (Marini and Mantegazza 2010; Guerrini et al. 2014), with hundreds of mutations reported thus far in different epilepsy syndromes characterized by variable phenotypes, and is also the target of some familial hemiplegic migraine (FHM-type III) mutations; see www.molgen.ua.ac.be/SCN1AMutations and <http://www.scn1a.info/> for *SCN1A* variant databases. The most severe epileptic phenotype associated with Na_v1.1 mutations is Dravet syndrome (DS), also known as Severe Myoclonic Epilepsy of Infancy (SMEI), an extremely severe epileptic encephalopathy (i.e. a disorder in which it is hypothesized that epileptic seizures and epileptiform activity impair brain function, although this causal link has not been clearly demonstrated yet). DS is characterized by onset in the first year of life as prolonged seizures triggered by fever and later appearance of severe afebrile seizures of various type, drug resistance, ataxia, delayed psychomotor development, cognitive impairment and behavioral dysfunctions (Dravet et al. 2005). In general, it is caused by de novo deletions or missense mutations of Na_v1.1 (Claes et al. 2001; Depienne et al. 2009), which are found in >80% of patients.

Genetic (Generalized) Epilepsy with Febrile Seizures Plus (GEFS+) patients shows large phenotypic heterogeneity in families, including febrile seizures (FS) and febrile seizures plus (FS+: FS after 6 years of age). The course and response

are indicated below the diagram of the protein. Nav voltage-gated Na⁺ channels, Cav3.2 voltage-gated Ca²⁺ channels, T-type-1H, Kv7 voltage-gated K⁺ channels, M-type, KCa4.1 Na⁺-activated K⁺ (KNa) channel, SLACK-SLO2.2 type; GABA-A gamma-aminobutyric acid receptor, type A, Ach nicotinic acetylcholine receptor, NMDA glutamate receptor, N-methyl-D-aspartate (NMDA) type, DS Dravet syndrome, GEFS+ generalized (genetic) epilepsy with febrile seizures plus, EE epileptic encephalopathies, BFNIS benign familial neonatal-infantile seizures, BNIS benign neonatal familial seizures, IGE idiopathic generalized epilepsies, MMPSI malignant migrating partial seizures of infancy, ADNFLE autosomal dominant nocturnal frontal lobe epilepsy, EAS epilepsy-aphasia syndromes

to antiepileptic drugs may be considerably variable within the same family: some patients experience rare febrile or non-febrile seizures that remit after a few years, while others, even within the same family, have drug resistant epilepsy, with Dravet syndrome as the extreme of the spectrum (Scheffer and Berkovic 1997). GEFS+ was originally recognized thanks to large autosomal dominant pedigrees with 60–70% penetrance, but it is likely that most cases occur in small families or are sporadic. It is caused in general by missense $\text{Na}_v1.1$ mutations, which are found in about 10% of families (Marini and Mantegazza 2010).

$\text{Na}_v1.1$ mutations have also been identified in some patients presenting with different epileptic encephalopathies, ranging from Lennox-Gastaut syndrome to epilepsy aphasia syndrome (Depienne et al. 2009; Marini and Mantegazza 2010; Carvill et al. 2013b; Guerrini et al. 2014). One of the mildest epileptic phenotypes associated with missense $\text{Na}_v1.1$ mutations is benign simple febrile seizures (sFS) (Mantegazza et al. 2005), although some patients of this family developed also mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE&HS). Interestingly, genome-wide association studies have linked *SCN1A* single nucleotide polymorphisms (rs7587026 and rs11692675) to development of MTLE&HS upon a history of febrile seizures (Kasperaviciute et al. 2013), and a further *SCN1A* polymorphism has been identified as risk factor for idiopathic/genetic generalized epilepsies (rs11890028) (Steffens et al. 2012). Familial hemiplegic migraine (FHM) is a rare severe autosomal dominant inherited subtype of migraine with aura characterized by hemiparesis during the attacks (Vecchia and Pietrobon 2012). Some FHM families carry missense $\text{Na}_v1.1$ mutations, in some cases without any signs of epileptic phenotypes (Cestele et al. 2013a).

In vitro functional studies of missense epileptogenic $\text{Na}_v1.1$ mutations in heterologous systems have initially shown controversial results (Mantegazza et al. 2010b; Mantegazza 2011), revealing both gain- and loss-of-function effects, but loss-of-function seems to be the predominant mechanism of action of both truncations and missense mutations. In fact, consistently with the phenotype of DS patients, mouse models of $\text{Na}_v1.1$ truncating DS mutations exhibit spontaneous seizures, cognitive impairment and reduction of Na^+ current selectively in GABAergic inhibitory interneurons, causing reduction of their excitability and of GABAergic inhibition, leading to network hyperexcitability (Yu et al. 2006; Ogiwara et al. 2007; Han et al. 2012; Ito et al. 2012; Liautard et al. 2013). $\text{Na}_v1.1$ truncations lead to haploinsufficiency without negative dominance (Bechi et al. 2012). Studies of animal models have confirmed that also GEFS+ mutations cause loss of function of $\text{Na}_v1.1$ and induce reduced excitability of GABAergic neurons (Tang et al. 2009; Martin et al. 2010).

Although some light has been shed on the pathomechanism of $\text{Na}_v1.1$ mutations, the causes of the striking phenotypic variability observed in some patients are still not clear. For instance, some $\text{Na}_v1.1$ mutations can cause phenotypes extending from different types of epilepsy to familial hemiplegic migraine (Cestele et al. 2013b). Some of the phenotypic variability can be linked to the combined action of mutations/variants in different genes. It has been shown that a $\text{Na}_v1.1$ missense mutant, identified in families with extreme phenotypes comprising Dravet syndrome,

causes loss of function because of folding defects that can be rescued by molecular interactions with associated proteins or pharmacological chaperones (Cestele et al. 2008). These results have been confirmed and extended to typical GEFS+ families and Dravet syndrome patients with de novo mutations (Rusconi et al. 2009; Sugiyama et al. 2012; Thompson et al. 2012). This mechanism may generate phenotypic variability because of genetic background-dependent variability in rescue, and also be possibly used in the development of therapeutic approaches. As recently shown for a missense *SCN1A* mutant identified in a family with pure FHM (Cestele et al. 2013a), rescue of folding defects may also transform non-functional loss of function mutants (effect that is consistent with severe epilepsy) into gain of function ones, effect that is consistent with familial hemiplegic migraine (Cestele et al. 2008). Genetic background can modulate also the effect of $\text{Na}_v1.1$ truncating mutations, because there are reports of mild phenotypes or no phenotype in some individuals carrying these mutations (Orrico et al. 2009; Klassen et al. 2011).

Rare mutations in the *SCN1B* gene, coding for the Na^+ channel $\beta 1$ subunit have been identified in both GEFS+ (Wallace et al. 1998; Meadows et al. 2002) and DS (Patino et al. 2009).

Similarly, few mutations of the *GABRG2* gene (coding the $\gamma 2$ subunit of the gamma-aminobutyric acid receptor type A, GABA-A, ionotropic heteropentameric receptor of the main inhibitory neurotransmitter of the brain) can cause GEFS+, sometimes with DS phenotypes (Baulac et al. 2001). Functional expression of some *GABRG2* mutations, identified in patients with GEFS+, revealed a pronounced loss-of-function by altered gating or defective trafficking and reduced surface expression as a common pathogenic mechanism (Macdonald et al. 2010). Knock-in mouse models of the R43Q *GABRG2* mutation shows generalized seizures and reduced GABAergic inhibition (Chiu et al. 2008). Recently, also mutations of the *GABRA1* gene (coding for the $\alpha 1$ subunit of the GABA-A receptor) have been identified in few Dravet syndrome patients (Carvill et al. 2014). Hence, these mutations could reduce GABAergic neurotransmission, the main mechanism for neuronal inhibition in the brain, similarly to *SCN1A* mutations, which may explain the occurrence of seizures.

Mutations of the SCN2A Voltage Gated Na^+ Channel and of KCNQ2-KCNQ3 K^+ Channels: An Unexpected Spectrum of Severity

SCN2A/ $\text{Na}_v1.2$, KCNQ2 and KCNQ3 have been initially involved in mild benign epilepsies of newborns and infants, but more recently their mutations have also been linked to severe epileptic encephalopathies, showing a spectrum of severity that is similar to that observed for $\text{Na}_v1.1$ mutations.

K^+ channels are composed by four subunits forming the ion-conducting pore and generate repolarizing currents that oppose depolarizing currents generated by, e.g. Na^+ channels. KCNQ channels, which consist of homomeric or heteromeric

tetramers, are responsible for the so called M-current (muscarinic receptor regulated), which is a non-inactivating K^+ current that activates at subthreshold membrane potentials counteracting membrane depolarizations that would lead to action potential generation. Thus, it plays an important role in influencing neuronal firing activity, limiting spiking frequency and reducing the responsiveness to synaptic inputs. *KCNQ2* and *KCNQ3* form a heteromeric K^+ channel (Fig. 1), which is particularly important in the axon initial segment and nodes of Ranvier of glutamatergic neurons (Delmas and Brown 2005).

Mutations or deletions/duplications involving one or more exons of *KCNQ2* and, in a smaller number of patients, mutations of *KCNQ3* have been identified in benign familial neonatal seizures (BFNS) (Biervert et al. 1998; Singh et al. 1998; Singh et al. 2003). BFNS is characterized by clusters of seizures that appear from the first days of life up to the third month to spontaneously disappear after weeks to months. Seizures have focal onset, often with hemi-tonic or hemiclonic symptoms or apneic spells, or can clinically appear as generalized. Interictal EEG is usually normal. The risk of seizures recurring later in life is about 15% (44). Functional studies in in-vitro systems performed co-expressing heteromeric wild-type and mutant *KCNQ2/3* channels revealed a reduction of about 20–30% in the resulting K^+ current, which is apparently sufficient to cause BFNS (Maljevic et al. 2008). Although the reduction of the K^+ current can cause epileptic seizures by subthreshold membrane depolarization, which increases neuronal firing, it is not fully understood why seizures preferentially occur in neonates (Weber and Lerche 2008). It is possible that the neonatal brain is more vulnerable to changes, even small, of neuronal excitability. Alternatively, *KCNQ2* and *KCNQ3* channels, when mutated, might be replaced by other K^+ channels that become functional after the first months of life. Transgenic and knock-in BFNS mice have been generated. Transgenic mice expressing a dominant negative *KCNQ2* mutant (Peters et al. 2005) show spontaneous partial and generalized tonic-clonic seizures, but also pronounced hyperactivity and cell loss in the hippocampus, with impaired hippocampus-related memory, which are not consistent with the typical BNFS human phenotype. Knock-in mice of *KCNQ2* A306T or G311V mutations (Singh et al. 2008) show spontaneous tonic-clonic seizures and, consistently with BNFS, no hippocampal neurodegeneration; however, only homozygous mice manifest epilepsy and they also tend to have seizures in adulthood.

Mutations in *SCN2A*/ $Na_v1.2$ have been identified in benign familial neonatal-infantile seizures (BFNIS) (Berkovic et al. 2004). BFNIS are characterized by seizures similar to those observed in children with BFNS, but age at seizure onset ranges from the neonatal period to infancy in different family members, with a mean onset age of 3 months. In general, remission occurs by 12 months with a very low risk of later seizures. $Na_v1.2$ (Fig. 1) is particularly important for the excitability of the axon initial segment and nodes of Ranvier in glutamatergic neurons early in development. Mutations causing BFNIS have been studied in both transfected neocortical neurons and cell lines identifying gain of function effects (Scalmani et al. 2006; Liao et al. 2010) consistent with hyperexcitability of excitatory neurons. The remission may depend on a developmental switch between $Na_v1.2$ and $Na_v1.6$

in myelinated axons that occur at early developmental stages (Scalmani et al. 2006; Liao et al. 2010). No animal models reproducing a BFNIS mutation have been developed yet.

Similarly to $\text{Na}_v1.1$ mutations, *KCNQ2* and $\text{Na}_v1.2$ mutations can cause a wide phenotypic spectrum that includes severe epileptic encephalopathies. In particular, *KCNQ2* mutations have been identified in severe neonatal epileptic encephalopathies associated with intellectual disability and motor impairment, with a burst-suppression EEG pattern or multifocal epileptiform activity, but also in milder forms (Weckhuysen et al. 2012; Weckhuysen et al. 2013). Functional studies of these mutations have been recently performed in *Xenopus* Oocytes, showing that they can have more severe loss of function than those causing BFNIS (Miceli et al. 2013) or, in some cases, they can cause negative dominance inhibiting function of wild type *KCNQ2* (Orhan et al. 2014). A transgenic mouse model expressing a *KCNQ2* dominant negative mutant may model these forms (Peters et al. 2005).

Similarly, de novo $\text{Na}_v1.2$ truncating and missense mutations have been identified in early onset intractable childhood epilepsies, with features ranging from Ohtahara syndrome to Dravet syndrome (Lossin et al. 2012; Nakamura et al. 2013; Touma et al. 2013). Contrary to BFNIS mutants, functional analysis of some of these mutants using in-vitro expression systems has shown loss of function (Lossin et al. 2012), although it is not yet clear how loss-of-function in a Na^+ channel predominantly expressed in excitatory neurons would lead to network hyperexcitability. Notably, a loss of function *Scn2a* knockout mouse does not show an overt epileptic phenotype, although this has not been studied in detail (Planells-Cases et al. 2002).

Neuronal Nicotinic Acetylcholine Receptors and KCNT1 K^+ Channel Mutations in Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Neuronal nicotinic acetylcholine receptors (nAChR) have important neuromodulatory functions (including modulation of GABA and glutamate release, the main inhibitory and excitatory neurotransmitters of the brain, respectively) and consist of homo- or heteromeric pentamers of various combinations of at least 17 subunits: $\alpha1$ —10, $\beta1$ —4, δ , ϵ and γ . The $\alpha4$ - $\beta2$ combination is the most common in the thalamus and cerebral cortex. A mutation in the gene *CHRNA4*, encoding the $\alpha4$ -subunit of a neuronal nicotinic acetylcholine receptor (nAChR), was the first ion channel mutation found in an inherited form of epilepsy (Steinlein et al. 1995): autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). About 15 mutations in *CHRNA4*, five in *CHRN2*, which encodes the $\beta2$ -subunit of nAChR, and one in *CHRNA2*, encoding the neuronal nAChR $\alpha2$ -subunit, have been reported so far and account for <10% of the tested ADNFLE families (Ferini-Strambi et al. 2012). All the identified mutations are located in the pore-forming M2 transmembrane segments.

ADNFLE includes frequent, usually brief, seizures with onset on average at around 10 years of age, with hyperkinetic or tonic manifestations, typically in clusters at night during slow-wave sleep. Paroxysmal arousals, dystonia-like attacks and epileptic nocturnal wanderings are also part of the phenotype. Functional studies of nAChR have produced controversial results, which make the underlying pathogenic mechanisms still unclear. Expression of $\alpha 4$ mutants in heterologous systems resulted in various effects consistent with either gain or loss of function: increased sensitivity to acetylcholine (gain of function); decreased Ca^{2+} potentiation or accelerated desensitization (loss of function) (Bertrand et al. 2002). Mutations of $\beta 2$ showed gain of function by increased sensitivity to acetylcholine or slower desensitization (De Fusco et al. 2000) and the $\alpha 2$ mutation showed gain of function by increased sensitivity to acetylcholine (Aridon et al. 2006). The $\alpha 4$ mutations S252F and +L264 engineered in knock-in mice (Klaassen et al. 2006) induced spontaneous seizures of various types, in some cases similar to those of the human phenotype, but no paroxysmal arousal and dystonia-like manifestations; whereas the $\alpha 4$ subunit S248F knock-in mice show no spontaneous seizures but nicotine-induced dystonic attacks (Teper et al. 2007). $\alpha 4$ -subunit S284L transgenic rats (Zhu et al. 2008) show a more complete ADNFLE phenotype, with spontaneous attacks during slow-wave sleep, comprising of paroxysmal arousals (frightened behavior), dystonic activity and epileptic wandering. Notably, the pathogenic mechanisms are also different in these models: upon application of nicotine, GABAergic inhibition is increased in frontal cortex of S252F and +L264 knock-in mice (Klaassen et al. 2006), whereas it is reduced in somatosensory cortex of S284L transgenic rats (Zhu et al. 2008).

Missense mutations in the Na^+ -activated K^+ channel gene *KCNT1* (KCa4.1-SLACK-SLO2.2 type; Fig. 1) have been recently reported in 4 unrelated families with a severe form of ADNFLE (Heron et al. 2012). *KCNT1* is activated by the inward flux of Na^+ ions during neuronal firing and its activity contributes to the slow hyperpolarization that follows repetitive firing. Thus, its action negatively modulates high frequency firing. There is no information about the effect of its ADNFLE mutations because functional analysis was not performed. Patients had an earlier mean age of onset (6 years) compared to other ADNFLE forms and frequently exhibited psychiatric features and intellectual disability. Thus, the phenotype has some features that are typical of epileptic encephalopathies and, interestingly, mutations of *KCNT1* have also been identified in the epileptic encephalopathy malignant migrating partial seizures in infancy (see below).

Therefore, genetic variability is evident in this clinically relatively homogenous epileptic form.

Ion Channel Mutations Recently Identified with Whole Exome Sequencing Studies

Current efforts of whole exome sequencing (WES) are generating a great amount of information that is improving our understanding of the pathophysiology of genetic epilepsies, in particular for rare epileptic encephalopathies. Most of the mutations

that have been thus far interpreted as causative arise as de novo mutations or are inherited in an autosomal recessive fashion, often as compound heterozygous mutations. Notably, mutations in these new epilepsy genes associated with epileptic encephalopathies with variable phenotypes, occasionally resembling known syndromes including Dravet syndrome, are found in a small number of patients (Allen et al. 2013; Carvill et al. 2013b; Suls et al. 2013). Although mutations in non-ion channel genes have been identified, genes coding for ion channels are still common ones. For instance, mutations of the *HCN1* gene (coding for the type 1 subunit of the hyperpolarization-activated, cyclic nucleotide-gated channel that contributes to the cationic I_h current in neurons and can regulate the excitability of neuronal networks) have been identified in patients with Dravet syndrome-like phenotypes (Nava et al. 2014). Mutations of *SCN8A*/ $\text{Na}_v1.6$ are associated with other types of early onset epileptic encephalopathies (109, 112); this is the fifth Na^+ -channel gene to be mutated in epilepsy when variants of *SCN3A*/ $\text{Na}_v1.3$ are included (Vanoye et al. 2014; Fig. 1).

Mutations in the *GRIN2B* gene (encoding the NR2B subunit of the heterotetrameric N-methyl-D-aspartate, NMDA, receptor, a ionotropic receptor of the main excitatory neurotransmitter of the brain: glutamate) have also been recently identified in 3 patients with phenotypes that include West syndrome and focal epilepsy with intellectual disability (Lemke et al. 2014).

Mutations in the *GRIN2A* gene encoding the NR2A subunit of the NMDA glutamate receptor have been identified in epilepsy-aphasia syndromes (EAS), which are a group of severe epileptic encephalopathies with a characteristic EEG pattern and developmental regression particularly affecting language that include Landau-Kleffner Syndrome (LKS) and continuous spike-waves in slow sleep (CSWS); functional analysis of these mutations using in-vitro systems has shown gain of function (Carvill et al. 2013a; Lemke et al. 2013; Lesca et al. 2013). Phenotypes of *GRIN2A* patients appear to be very different from those of *GRIN2B* mutations.

WES and targeted sequencing studies have also showed that ion channel genes previously associated with milder phenotypes can also cause epileptic encephalopathies in some patients (Carvill et al. 2013b), including *GABRA1* (coding for the $\alpha 1$ subunit of the GABA-A receptor), which has been previously involved in mild idiopathic generalized epilepsy (see below) and, as highlighted above, *SCN2A* Na^+ channel and *KCNQ2* K^+ channel genes. Similarly, de-novo gain of function mutations in the *KCNT1* gene have been identified in patients with malignant migrating partial seizures of infancy (MMPIS), a rare syndrome with infantile onset intractable and migrating focal seizures with severe impairment of psychomotor development (Barcia et al. 2012), but *KCNT1* mutations have also been associated to other and very different epilepsy phenotypes, including autosomal dominant nocturnal frontal lobe epilepsy (Heron et al. 2012) (see above).

Epilepsy Towards the Next Decade

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