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REVIEW ARTICLE

Epilepsy and brain channelopathies from infancy to adulthood

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Abstract

Genetic brain channelopathies result from inherited or de novo mutations of genes encoding ion channel subunits within the central nervous system. Most neurological channelopathies arise in childhood with paroxysmal or episodic symptoms, likely because of a transient impairment of homeostatic mechanisms regulating membrane excitability, and the prototypical expression of this impairment is epilepsy. Migraine, episodic ataxia and alternating hemiplegia can also occur, as well as chronic phenotypes, such as spinocerebellar ataxias, intellectual disability and autism spectrum disorder. Voltage-gated and ligand-gated channels may be involved. In most cases, a single gene may be associated with a phenotypical spectrum that shows variable expressivity. Different clinical features may arise at different ages and the adult phenotype may be remarkably modified from the syndrome onset in childhood or adolescence. Recognizing the prominent phenotypical traits of brain channelopathies is essential to perform appropriate diagnostic investigations and to provide the better care not only in the paediatric setting but also for adult patients and their caregivers. Herein, we provide an overview of genetic brain channelopathies associated with epilepsy, highlight the different molecular mechanisms and describe the different clinical characteristics which may prompt the clinician to suspect specific syndromes and to possibly establish tailored treatments.

Keywords Epilepsy · Ion channels · Channelopathies · Mutations · Next generation sequencing

Introduction

The term ‘channelopathy’ encompasses a wide spectrum of disorders underpinned by genetic or acquired dysfunction of ion channels [1].

Ion channels are proteins located across the lipid bilayer of cell membranes, wherein they form a pore to facilitate the inflow or outflow of ions according to their electrochemical gradient.

Each channel exhibits a selective permeability to specific ions, whose trafficking is gated by the channel state: open, inactivated closed and resting closed. The gating may be controlled by transmembrane electric potential (*voltage-gated channels*), specific extracellular ligand molecules (*ligand-gated channels*), or else different mechanisms such as intracellular second messengers, light, temperature and mechanical stimuli. Ion pumps similarly modulate ion trafficking, albeit

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with a different mechanism, i.e. ions are moved against gradient through active transport to maintain the resting potential. Most ion channels exhibit a heteromeric structure with a pore-forming subunit and accessory regulatory subunits. Ion pumps are similar heteromeric proteins with a catalytic main subunit as well as auxiliary and regulatory subunits.

Genetic channelopathies have been described in diverse systemic disorders, consistent with the widespread expression of ion channels and ion pumps and with their role in regulating the resting potential, signal transduction, size, growth, motility and apoptosis of all eukaryotic cells. There exists a tissue selectivity of ion channels; hence, most genetic channelopathies are confined to the system wherein the related ion channel is mainly expressed. Indeed, most of ion channel genes are enriched in the brain, wherein their dysfunction is especially detrimental to neurons, by affecting the generation, suppression and spread of the action potential [2, 3]. The transient and recurrent impairment of membrane excitability may lead to paroxysmal symptoms, especially seizures, but their occurrence may vary over time due to the different expression of ion channels at different ages [4]. Indeed, the history of epilepsy genetics has long been dominated by inherited channelopathies. The first gene found in familial epilepsy was *CHRNA4*, encoding for a subunit of the ligand-gated nicotinic acetylcholine receptor and causing autosomal dominant frontal lobe epilepsy [5]. Thereafter, a growing number of mutations affecting ion channel genes have been identified in neurological disorders, including familial and sporadic epilepsies.

Specific syndromes associated with single ion channel genes are well described; however, the large-scale application of next generation sequencing (NGS) has revealed the genotype-phenotype correlation may be extremely challenging. Ion channel genes initially associated only with benign phenotypes (e.g. *KCNQ2*, *SCN2A*) have also been demonstrated to be implicated in severe epileptic encephalopathies.

To be able to diagnose a specific genetic aetiology in epilepsy carries substantial benefit in both children and adults. Families are often relieved to find a cause usually after a distressing diagnostic odyssey. Unnecessary invasive testing can be avoided and appropriate familial counselling can be established [6]. Furthermore, the comprehension of the underlying molecular biology raises the possibility of delivering precision medicine by using drugs that reverse or counteract the specific ion channel dysfunction [7].

Herein, we overview the molecular pathogenesis and the phenotype of genetic brain encephalopathies associated with epilepsy, highlighting the different clinical characteristics which may prompt the clinician to suspect specific syndromes and discussing the specific clinical challenges at different ages of presentation.

Methods

We performed a PubMed/Medline search for articles up to and including May 2019 using Boolean logic with the following terms: 'brain AND channel*', 'seizure AND channel*', 'epilepsy AND channel*', 'encephalopathy AND channel*' with no language restrictions. We integrated the items retrieved by the automated query with selected references manually searched on PubMed, Embase, the Human Gene Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), Google (https://www.google.com) and Google Scholar (https://scholar.google.com) search engines.

We then analysed the available data for the two main types of ion channels.

Voltage-gated channels

Sodium channels

Voltage-gated sodium channels ('VGSCs' or 'Nav channels') are heteromeric complexes consisting of a large central pore-forming alpha subunit and two smaller auxiliary beta subunits. A superfamily of genes clustering on chromosome 2 encodes for different isoforms of the alpha subunit (Nav1.1-Nav1.9). All alpha subunits comprise four homologous domains (I–IV), each containing six transmembrane segments (S1–S6). The S5–S6 segments of each domain form the pore, whilst the S4 segment acts as a voltage sensor. The depolarization of the cell membrane leads to a conformational change of the channel, resulting in a sodium inflow which triggers action potentials in nerve, muscle and other excitable cells [8].

Mutations in three alpha subunit genes, all highly expressed in the central nervous system (*SCN1A*, *SCN2A*, *SCN8A*), have been shown to cause epilepsy in humans [9] (Fig. 1).

SCN1A encodes for the alpha 1 subunit (Nav1.1), whose expression sharply increases from 4 to 5 months of age [10]. Mutations of this gene yield distinct phenotypes sharing a peculiar fever sensitivity. Pathogenic variants of *SCN1A* were initially found in genetic epilepsy with febrile seizures plus (GEFS+), an autosomal dominant disorder characterized by variable intra-familial phenotypical expression. Affected family members may exhibit febrile seizures persisting beyond 6 years of age as well as focal or generalized seizures, but with normal cognitive functioning [9] (Figs. 1 and 2). De novo heterozygous *SCN1A* mutations were later identified in a more severe phenotype, Dravet syndrome [11]. Indeed *SCN1A* is the most frequently mutated gene in epileptic encephalopathies; de novo mutations have been identified in 2.8% of trios investigated by exome sequencing in the Epi4k study [12] and *SCN1A* was the only gene that reached exome-wide significance in the Epi25 study of ultra-rare variants in epilepsy

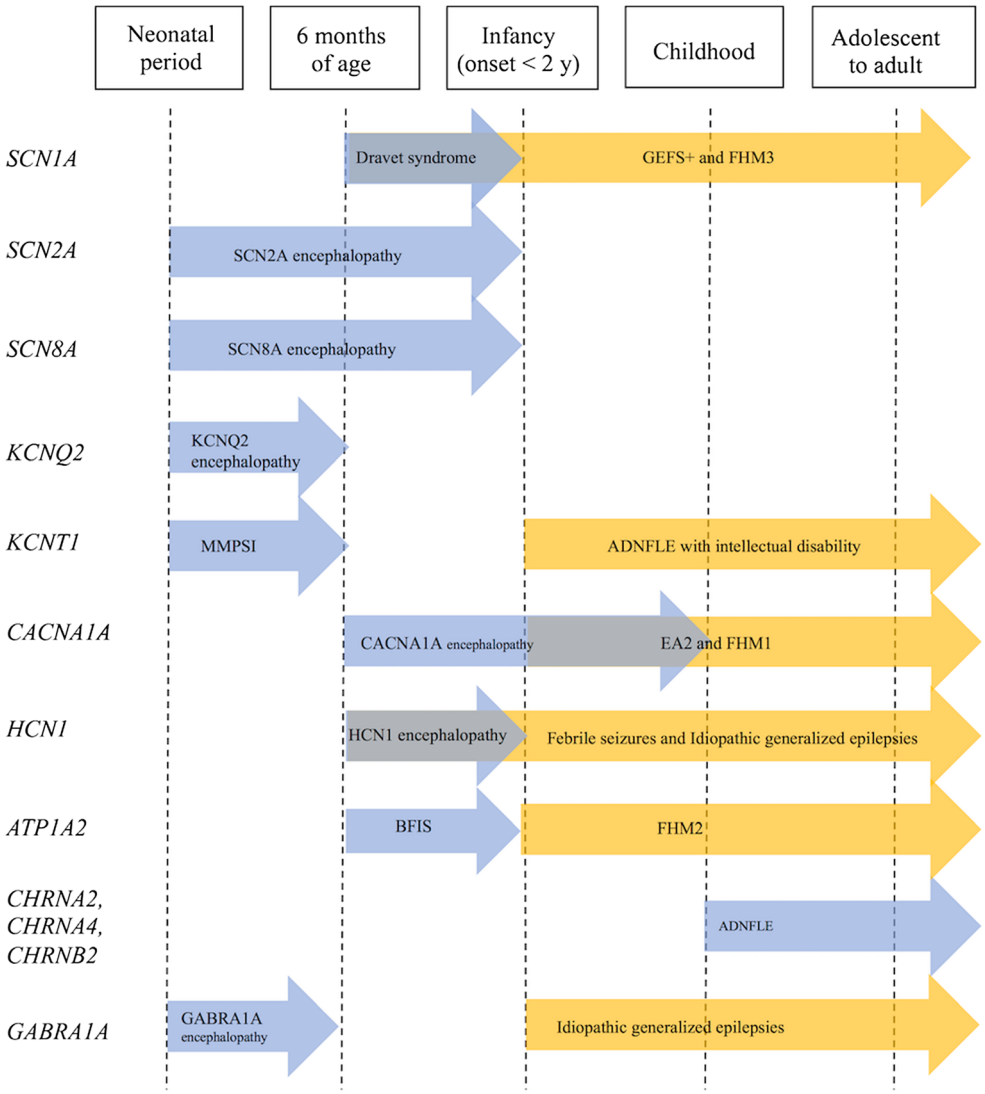

Fig. 1 Age of onset and related phenotypes of brain channelopathies (paediatric onset in cyan, adult onset in yellow)

(odds ratio = 18.4, comparing individuals with developmental and epileptic encephalopathies to healthy controls) [13].

The mutations identified in GEFS+ are missense with either gain or loss-of-function effect. Dravet syndrome-related mutations may be truncating mutations, splice-site mutations, frameshift intragenic deletions or gene duplications leading to haploinsufficiency or they may be missense mutations affecting the pore-forming region of the protein [14]. The underlying pathogenesis has been hypothesized to result from a reduction of the sodium current density in inhibitory interneurons rather than in pyramidal cells, leading to a net hyperexcitatory effect [15].

Dravet syndrome typically develops with the sudden onset of febrile seizures at 5–8 months of age in previously healthy children. Unlike simple febrile convulsions, these febrile seizures are often unilateral and very prolonged, sometimes leading to status epilepticus [16]. In about a third of cases, such an abrupt onset occurs after a vaccination [17] and indeed most cases formerly interpreted as alleged 'vaccine encephalopathy' were patients with previously undiagnosed Dravet syndrome [18]. During the first year of life, both febrile and afebrile seizures occur. From the second year of age, an overt encephalopathy is established. Developmental delay is accompanied by polymorphic seizure types including generalized tonic-clonic, alternating unilateral clonic, focal with impaired awareness, brief myoclonic, tonic (rare) or myoclonic non-convulsive status epilepticus described as 'obtundation status' [16, 19, 20]. Increased body temperature remains the most important seizure precipitant, whether caused by fever, warm baths, ambient warmth or physical exercise [21]. Seizures are also typically precipitated by the use of antiepileptic drugs that are sodium channel blockers (e.g. carbamazepine, phenytoin, lamotrigine). The EEG shows generalized spike-wave and polyspike-wave activity with multifocal discharges as well as a progressive slowing of the background activity. Photosensitivity is common, may be very early

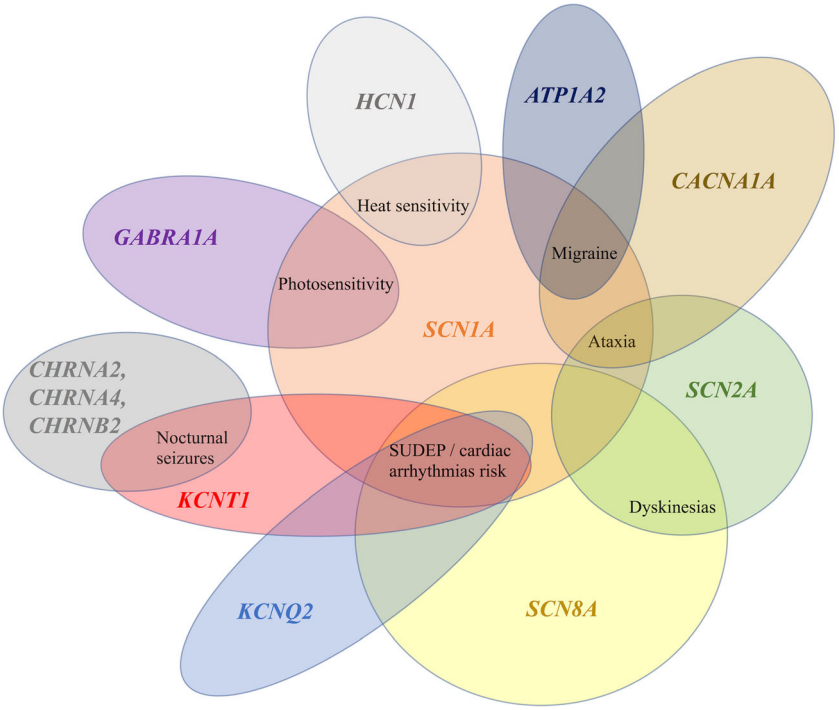

Fig. 2 Overlapping phenotypical traits of different brain channelopathies

(median age at onset, 1.25 years) and transient [22]. Some older patients may auto-induce seizures by voluntary eye closure [16, 21]. Children with Dravet syndrome typically start to walk and talk at a normal age but soon develop a wide-based ataxic gait and an impairment of language production skills, in spite of relative preservation of comprehension [16]. They may also have behavioural disturbances, impaired attention and autistic traits [23]. After 5 years of age, epilepsy tends to improve with stabilization of intellectual functioning and behaviour [16, 19, 24]. There is a high rate of early mortality, especially due to accidents, drowning, severe status epilepticus, infections and sudden unexplained death in epilepsy (SUDEP) [16].

In adulthood, seizures become less aggressive and temperature-sensitive (Table 1). Myoclonic and absence seizures disappear and convulsive seizures occur mainly in sleep along with tonic seizures. The EEG may show multifocal interictal discharges (Online Resource 1). Cerebellar features become more prominent, especially ataxia, dysarthria and intention tremor [25, 26]. Adults with Dravet syndrome can also develop characteristic levodopa-responsive extrapyramidal signs, such as axial dystonia and anterocollis with a crouching gait [27]. Gait disturbance may also be exacerbated by the onset of an axonal motor neuropathy [28].

Familial hemiplegic migraine type 3 (FHM3) is an alternative *SCN1A* allelic disorder associated with missense mutations; patients with FHM3 may rarely exhibit concomitant seizures [29, 30] (Figs. 1 and 2).

The *SCN2A* gene encodes for the $Na_V1.2$ channel, which is highly expressed in the initial axonal segments of excitatory hippocampal and cortical neurons from the birth [31]. Mutations of *SCN2A* were initially found in families with 'Benign familial neonatal-infantile seizures' (BFNIS), characterized by self-limiting epilepsy arising in early infancy and a favourable cognitive outcome [32, 33]. Thereafter, de novo *SCN2A* mutations have been increasingly recognized as a major cause of epileptic encephalopathies [32, 34] and linked to non-syndromic intellectual disability [35, 36] and autism spectrum disorders [36, 37]. De novo mutations of *SCN2A* have been identified in 0.8% of probands with epileptic encephalopathies in the Epi4k study [12].

Most patients with epilepsy and *SCN2A* mutations exhibit seizures from the first week of life, possibly due to the timing of $Na_V1.2$ channel expression, which peaks during early development and is then gradually replaced by $Na_V1.6$ (*SCN8A*) during the first months of life [31]. Less frequently, epilepsy arises during childhood, accompanied by cognitive regression and autistic features [32, 33] (Fig. 1). Recent findings suggest children with neonatal-onset seizures mainly have gain-of-function missense mutations and a good response to sodium channel blocking anti-epileptic drugs, whilst those with later onset epilepsy mostly have loss-of-function missense or truncating variants and do not respond to sodium channel blockers [33]. In patients with autism or intellectual disability, most identified mutations are truncating [37]. Although the $Na_V1.2$ channel appears to be mainly involved in childhood disorders, an *SCN2A* mutation with incomplete penetrance has also been recently identified in two siblings with juvenile onset myoclonic seizures and ataxia [38]. Follow-up data on the *SCN2A* encephalopathy suggest patients may develop

Table 1 Reported phenotypes of the most common brain channelopathies causing epilepsy

Ion channel gene	Related phenotypes	Childhood features	Clinical course at long-term and adulthood phenotype
SCN1A			
	GEFS+	Febrile seizures	Febrile and afebrile seizures, focal and generalized epilepsy, mostly normal intellectual functioning
	Dravet syndrome	Prolonged febrile and afebrile seizures, heating-sensitivity, ataxia, cognitive decline, autistic traits	Milder and less heating-sensitive epilepsy, levodopa responsive dystonia and anterocollis, ataxia, axonal motor neuropathy
SCN2A			
	Benign familial neonatal-infantile seizures	Focal seizures until 6 months of age	Seizure free, normal development
	SCN2A encephalopathy	Neonatal- infantile onset: focal and generalized seizures, gross developmental delay, possible migrating seizures and Ohtahara syndrome, ataxia, dyskinesias. Infantile onset: focal seizures, mild intellectual disability, dyskinesias Childhood onset: focal seizures, regression, autistic features	Focal seizures, intellectual disability, spastic tetraparesis, autistic traits, late-onset ataxia
SCN8A			
	Autosomal dominant familial benign infantile seizures	Afebrile focal or generalized tonic-clonic seizures at 1–2 years of life	Seizure free, rarely paroxysmal dyskinesia
	SCN8A encephalopathy	Infantile onset of focal, myoclonic and tonic seizures with autonomic signs, possible dystonic/dyskinetic movement disorders, ataxia, sleep disorders, risk of cardiac arrhythmias	Mild to severe intellectual disability, possible seizure freedom on sodium channel blockers, ataxia and extrapyramidal signs
KCNQ2			
	Autosomal dominant benign familial neonatal seizures	Neonatal afebrile seizures	Seizure freedom
	KCNQ2 encephalopathy	Neonatal stormy seizures with burst-suppression	Very rare seizures, intellectual disability, spastic tetraparesis in infancy
KCNT1			
	Autosomal Dominant Nocturnal Frontal Lobe Epilepsy with intellectual disability and behaviour disturbances	Nocturnal focal seizures arising in infancy/puberty and persisting in adulthood with possible intellectual disability and behaviour disturbances	
	KCNT1 encephalopathy (Malignant migrating partial seizures of infancy)	Sub-continuous multifocal and migrating seizures, acquired microcephaly, athetotic movements, hypotonia, strabismus, cardiac arrhythmias	Unknown
	Brugada syndrome (1 case)	Not reported	Reported in a single adult patient after loss of consciousness
CACNA1A			
	Idiopathic generalized epilepsy	Childhood absence epilepsy	Unclear
	Episodic ataxia type 2	Paroxysmal ataxia lasting between hours and a few days since childhood/puberty. Sometimes triggered by physical stress, infection, fever, heat, exertion, caffeine, or alcohol. Possible tonic-clonic and absence seizures	Chronic ataxia, nystagmus, cerebellar atrophy may develop
	Familial hemiplegic migraine type 1	Sudden onset of migraine with hemimotor/hemisensory symptoms lasting up to 72 h	Seizures may be triggered by migraine attacks, chronic ataxia, rarely parkinsonism
	CACNA1A encephalopathy (biallelic mutations)	Early onset seizures, intellectual disability, autistic features, progressive cerebral and optic nerve atrophy	Progression of childhood features and rare late onset cases
HCN1			
	HCN1 encephalopathy	Neonatal/infantile onset, heat sensitivity, prolonged febrile and afebrile seizures (Dravet-like)	Drug-resistant epilepsy and intellectual disability
	Sporadic and familial idiopathic generalized epilepsies	Febrile and afebrile seizures possible GEFS+ phenotype	Normal neurodevelopment or mild intellectual disability
ATP1A2			
	Benign familial infantile convulsions	Self-limited infantile seizures	Seizure freedom
CHRNA2, *CHRNA4, CHRNB2*			
	Autosomal dominant nocturnal frontal lobe epilepsy	Nocturnal focal seizures arising in infancy/puberty and persisting in adulthood (drug-resistant in about 30% of cases)	
GABRA1A			
	Sporadic and familial idiopathic generalized epilepsies	Photosensitive childhood absence epilepsy	Photosensitive juvenile myoclonic epilepsy/idiopathic generalized epilepsy
	Epileptic encephalopathies	Ohtahara syndrome, infantile spasms, Dravet-like phenotypes and myoclonic astatic epilepsy, with photosensitivity	Drug-resistant seizures and intellectual disability

episodic ataxia from infancy/puberty [39] or suffer persisting seizures, intellectual disability, autistic traits and stereotypies in adulthood [32] (Table 1, Figs. 1 and 2).

Heterozygous missense mutations of *SCN8A* have recently been associated with a spectrum of epilepsies, ranging from autosomal dominant familial benign infantile seizures (inherited mutations) to epileptic encephalopathies (de novo mutations in 0.8% of the Epi4k cohort) [12, 40, 41] (Fig. 1). The Epi25 study has recently disclosed a remarkable enrichment of ultra-rare variants in people with epilepsy compared with healthy subjects (odds ratio = 13.8), pinpointing *SCN8A* as a top ranking gene in epilepsy [13].

The *SCN8A* gene product (sodium channel subunit $Na_v1.6$) is increasingly expressed from the neonatal period, progressively replacing the $Na_{V1.2}$ channel in initial axonal segments. Accordingly, most patients with S*CN8A* mutations develop epilepsy in infancy (median age = 4 months) [40]. Patients with familial benign infantile seizures exhibit self-limited focal and generalized seizures up to 2 years of age; thereafter, epilepsy remits and neurodevelopment is normal in almost all cases [42]. Some of these patients may later develop episodes of paroxysmal dyskinesia from puberty [43] Conversely, those with *SCN8A*-related encephalopathy suffer global developmental delay and multiple intractable seizure types, which include focal, tonic with autonomic signs, clonic, myoclonic, absence and epileptic spasms [40, 44, 45]. Sleep disorders and frequent startles related to an hyperalert state have been reported [46]. An intermediate phenotype with treatable epilepsy and mild cognitive impairment has also been described [47]. Genotype-phenotype correlation is poor as patients harbouring the same mutation may have different clinical presentations [40]. Evidence from animal models of *SCN8A*-related encephalopathy suggests a high risk of fatal cardiac arrhythmias [48]. A movement disorder characterized by dystonic/dyskinetic attacks may develop both in patients with benign familial infantile seizures and in those with an epileptic encephalopathy, independently from the seizure course [40, 42]. There are also isolated case reports of adults with intellectual disability, ataxia and extrapyramidal signs [47] (Table 1). There is clinical evidence of a possible targeted efficacy of sodium channel blockers in SCN8A-related epilepsy, especially if the mutations are known to cause gain of function [49].

Potassium channels

Potassium channels are a large family of ubiquitous transmembrane proteins, each composed of four α subunits, which interlock to constitute the pore-forming region, and different accessory subunits. According to their structure and kinetics, potassium channels can be categorized as voltage-gated (Kv) channels, calcium-activated potassium channels, inwardly rectifying (Kir) channels and tandem pore domain (K2P) channels [50].

Most human potassium channelopathies involve the voltage-gated family (Kv). These channels feature six transmembrane domains per alpha subunit with a voltage sensor on the fourth transmembrane segment (S4). The channels open in response to neuronal depolarization, modulating the frequency and duration of action potential [50].

Mutations affecting the Kv channels encoded by *KCNQ2* [51] and *KCNQ3* [52] were initially identified in patients with autosomal dominant benign familial neonatal seizures, characterized by normal neurodevelopment and time-limited seizures starting at 2–8 days of life and remitting spontaneously within 12 months. Akin to many other channelopathies, the phenotypic spectrum has recently expanded to include severe phenotypes, namely families with drug-resistant seizures and intellectual disability harbouring *KCNQ2* [53] and *KCNQ3* [54] mutations as well as sporadic cases with a specific *KCNQ2*-epileptic encephalopathy [55] (Fig. 1).

The latter exhibit a characteristic epilepsy course, with drug-resistant tonic asymmetric, focal and clonic seizures in the first week of life, progressively disappearing in early infancy and remitting by the age of 1–3 years. There is a dynamic electroencephalographic pattern, with neonatal burst-suppression evolving to multifocal epileptiform activity during follow-up. In adulthood, patients suffer intellectual disability of variable severity, hypotonia and spastic tetraparesis.

[55] (Table 1). The pathophysiology of the divergence between the favourable seizure prognosis and the dismal neurodevelopmental outcome is possibly due to the different role of KCNQ2 channels in epileptogenesis and cognitive functioning. In neonates, potassium channels are the main source of inhibition; mutations of *KCNQ2* expose the newborn brain to a powerful excitatory drive, which is then mitigated by the growing role of GABAergic inhibitory transmission in early childhood [56]. The neurodevelopmental impairment may instead be related to the critical role of potassium channels in synaptic efficacy and learning-related gene expression in the cerebral cortex and hippocampus [57].

The severe encephalopathic phenotype is likely attributable to a dominant negative effect of *KCNQ2* mutations. The vast majority of mutations are missense and appear to cluster in four putative functional hotspots which would affect the conformation of the tetrameric subunits of the channel [58, 59]. Of note, to identify *KCNQ2* variants in severe epilepsies may assist the clinician in the therapeutic choice. The potassium channel opener retigabine may partially reverse the KCNQ2 loss of function and reduce seizure frequency [58], yet its production has been discontinued in 2017 due to safety issues. Sodium channel blockers appear effective in the active phase of epilepsy, possibly because sodium channels and KCNQ channels colocalize and interact at critical locations of the neuronal membrane [55, 59].

KCNQ2 mutations found in benign familial neonatal seizures are heterogeneous, including deletions in 20q13 affecting the whole gene and contiguous segments, and are randomly distributed throughout the channel structure [58].

Calcium-activated potassium channels are also implicated in epilepsy. These channels are located in axons and at presynaptic terminals of excitatory neurons. They are activated in response to the calcium influx during an action potential, thus hyperpolarizing the cell and limiting neuronal excitability. However, the functional effect of mutations affecting these channels is unclear. Gain-of-function mutations of *KCNMA1* ($K_{Ca}1.1$ channel) have been described in children with paroxysmal nonkinesigenic dyskinesia and early onset absences [60].

Mutations affecting inwardly rectifying potassium (Kir) channels have been demonstrated in patients with epilepsy. In particular, *KCNB1*, encoding for the main delayed rectifier channel of the hippocampus and cortex ($K_{v2.1}$), is an emerging gene in neurodevelopmental disorders. Mutations in this gene may produce a phenotypical spectrum including non-syndromic intellectual disability and an epileptic encephalopathy characterized by epileptic spasms, severe developmental delay, autism spectrum disorder and chronic drug-resistant epilepsy [61] .

De novo *KCNJ11* pathogenic variants affecting the inwardly rectifying Kir6.2 channel have also been associated with epilepsy and intellectual disability in patients with neonatal diabetes mellitus [62].

Specific severe epileptic phenotypes can result from mutations of *KCNT1*, which encodes a sodium-activated potassium channel subunit involved in the slow hyperpolarization that follows repetitive neuronal firing. Inherited missense mutations were initially reported in a severe form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE, see below, also known as autosomal dominant sleep-related hypermotor epilepsy) with intellectual disability and behavioural disturbances. De novo gain-of-function mutations have subsequently been found in about 40% of patients with malignant migrating partial seizures of infancy (MMPSI); in this syndrome, patients suffer nearly continuous multifocal seizures with migrating ictal EEG discharges in the first 6 months of life and then develop persistent drug-resistant seizures with acquired microcephaly, intellectual disability, axial hypotonia, pyramidal signs, extrapyramidal signs with athetoid movements and strabismus [63, 64] (Table 1, Figs. 1 and 2).

Further studies have demonstrated that the penetrance of *KCNT1* mutations is not complete and that different affected family members harbouring the same inherited variant may develop either autosomal dominant frontal lobe epilepsy or MMPSI. Clinical evidences suggest *KCNT1* may be considered an actionable gene, as about 30% of patients with both KCNT1-related phenotypes benefit from quinidine, an anti-arrhythmogenic potassium channel blocker, in terms of seizure control [63, 65]. Isolated cases of SUDEP and cardiac arrhythmias in patients with *KCNT1* mutations have been reported [66]. Even though the neurological phenotype in adults has not been described, a pathogenic *KCNT1* mutation has been reported in a 38-year-old patient with life-threatening Brugada syndrome by a cardiology team [67]; interestingly, this patient was diagnosed after sudden loss of consciousness interpreted as possible syncope or isolated seizure, raising the possibility of a mild epilepsy phenotype in adult age (Table 1).

None of these genes has been encountered in the Epi4k [12] and Epi25 [13] studies, mutations of potassium channels are likely less common than those of sodium channels.

Calcium channels

Voltage-gated calcium channels are composed of an α1 pore-forming subunit and several different subunits and they have a critical role in neuronal regulation of intracellular calcium concentration. Channel opening may result from either large membrane depolarization (*high voltage-activated channels:* HVA) or from small voltage changes (*low voltage-activated channels:* LVA), allowing the inflow of calcium ions according to their electrochemical gradient. Intracellular calcium modulates gene transcription, neurotransmitter release, neurite outgrowth and enzyme activity [68].

The HVA $Ca_{v2.1}$ (P/Q-type) channel, encoded by *CACNA1A*, is involved in neurological phenotypes. Heterozygous mutations of *CACNA1A* have been found in patients with epilepsy, ataxia or migraine (Table 1). Loss-of-function variants have been associated with two overlapping phenotypes, namely childhood absence epilepsy and episodic ataxia type 2. Patients with *CACNA1A*-related absence seizures may develop ataxic symptoms [69] and those with episodic ataxia have cerebellum-related paroxysmal symptoms (i.e. unsteadiness, vertigo, nystagmus) and may in turn develop tonic-clonic and absence seizures in 7% of cases [70]. Conversely, gain-of-function mutations may lead to familial hemiplegic migraine type 1, characterized by sudden onset of hemimotor and hemisensory symptoms lasting up to 72 h which can accompany, outlast or occur independently from a typical migrainous attack. These patients often have cerebellar symptoms and may develop unprovoked seizures in childhood and migraine-provoked seizures in adulthood [71] (Figs. 1 and 2). Late-onset parkinsonism has also been reported [72].

Biallelic *CACNA1A* mutations have been disclosed in patients with early onset seizures, intellectual disability, autistic features and progressive cerebral and optic nerve atrophy [73]. Moreover, *CACNA1A* de novo missense mutations have been identified in 1% of cases from a large cohort of epileptic encephalopathies [74].

Cerebellar dysfunction is a frequent phenotypical trait in patients harbouring *CACNA1A* mutations. The $Ca_{v2.1}$ channel is indeed especially important in cerebellar networks. In the mice model, *CACNA1A* deletions impair both the excitatory

drive of the granule cells on Purkinje cells and the neurotransmitter release by the Purkinje cells themselves, resulting in seizures and ataxia [75, 76]. In turn, the cerebellar dysfunction may influence cognitive functions. Disruption of the cerebellar projections to the prefrontal, frontal and limbic cortex may impair complex cognitive processes, interfering both with the default mode network and with motor memory learning and consolidation [77–79].

Not every *CACNA1A* mutation causes seizures: Patients with spinocerebellar ataxia type 6 (SCA6), caused by expansion of the CAG trinucleotide repeat sequence in this gene, do not develop epilepsy but rather a late-onset progressive ataxia, sometimes accompanied by pyramidal and extrapyramidal signs as well as peripheral neuropathy and autonomic disturbance [80].

Genes encoding for LVA channels, especially *CACNA1H*, are currently regarded as susceptibility genetic loci for human idiopathic generalized epilepsies in children and adolescents; this is not surprising considering that the murine model of absence epilepsy (*Generalized Absence Epilepsy Rat of Strasbourg*) exhibits *CACNA1H* variants [81].

HCN channels

Hyperpolarization-activated, cyclic nucleotide-gated (HCN) channels are a class of voltage-gated ion channels permeable to potassium and, to a lesser extent, sodium. Their kinetics are unique, as the channel is activated by cell hyperpolarization, remain open at negative voltages and their opening is potentiated by binding of cAMP. The brain isoform (HCN1) yields an inward depolarizing current named Ih ('hyperpolarization-activated' current) which drives the neuronal membrane potential back toward the threshold for calcium and sodium channel activation, hence modulating the neuronal excitability [82, 83].

The phenotypical spectrum of *HCN1* mutations spans from early onset encephalopathies to benign idiopathic generalized epilepsies [84–87]. Patients with sporadic mutations develop a neonatal/infantile onset epileptic encephalopathy in about a third of cases; in these subjects, epilepsy arises as prolonged febrile or afebrile seizures at a median age of 7 months and then progresses with drug-resistant tonic, tonic-clonic and seizures and intellectual disability. On the contrary, 42% of sporadic cases and the vast majority of familial cases exhibit milder phenotypes, such as transient febrile seizures, GEFS+, drug-responsive idiopathic generalized epilepsies with normal or borderline cognitive functioning [85] (Figs. 1 and 2).

Encephalopathic phenotypes are associated with pathogenic missense variants clustering within or close to transmembrane domains, milder phenotypes segregate with missense variants outside transmembrane domains, in the intracellular N- and C-terminal parts of the channel [85].

Ion pumps

Mutations affecting the function of ionic pumps can dysregulate the membrane potential and yield neuronal hyperexcitability. Neurological paroxysmal disorders can especially result from pathogenic variants of *ATP1A2*, which encodes the α2 subunit of the A1A2 glial sodium–potassium ATPase pump. Indeed, *ATP1A2* is the gene responsible of familial hemiplegic migraine type 2 (FHM2); up to 60% of patients with FHM2 may experience seizures, that usually start during childhood as febrile or afebrile seizures, sometimes preceding the first hemiplegic migraine attack, and have a benign evolution (i.e. benign familial infantile convulsions) [88, 89] (Figs. 1 and 2).

Ligand-gated channels

Nicotinic acetylcholine receptors

The first monogenic pathogenic variant to be identified in the history of epilepsy genetics affected a ligand-gated channel, namely the alpha-4 subunit of the nicotinic acetylcholine receptor encoded by *CHRNA4* in patients with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) [5] (Fig. 1). Beforehand, the ADNFLE syndrome had already been extensively described, yet the underlying pathophysiology was unknown. The disclosure of *CHRNA4* mutations in these patients highlighted the importance of ion channels in human epilepsy and paved the way for the concept of brain channelopathies [90]. Nowadays, we know ADNFLE may result from mutations affecting both the alpha (*CHRNA2*, *CHRNA4*) and the beta (*CHRNB2*) subunits of the receptor with a penetrance of about 70–80%. Most mutations are located in the pore-forming domain and act through a gain of function mechanism, although loss-of-function variants have also been reported [91, 92]. Seizures arise from about 10 years of age and typically occur in clusters during slow-wave sleep [91, 92]. They are stereotyped, frequent and brief. Seizure semiology comprises hyperkinetic or tonic seizures, paroxysmal arousals, dystonia-like attacks and epileptic nocturnal wanderings. Similar seizure phenotypes may be associated with mutations of unrelated genes such as *KCNT1* (see above), *CRH* and *DEPDC5* (reviewed in [93]). In childhood and adolescence, the differential diagnosis includes parasomnias, especially because seizures in ADNFLE may be accompanied by normal EEG recordings. However, parasomnias usually tend to spontaneously disappear in adult age; on the contrary, seizures in ADNFLE continue in adulthood if they are not recognized and they are drug-resistant in a third of cases [93] (Table 1). Many reports document sodium channel blockers as drugs of choice in ADNFLE, yet topiramate, acetazolamide, nicotine

transdermal patches and fenofibrate have also been efficacious in small case series (reviewed in [93, 94]).

GABA receptors

Mutations affecting GABA receptors have also been linked to epilepsy, not surprisingly, considering GABA is the main inhibitory neurotransmitter of the central nervous system. Most of the reported mutations affect genes for the GABA-A receptor, which is composed of five subunits. Missense mutations affecting either the alpha (*GABRA1*, *GABRA6*), beta (*GABARB3*), or gamma (*GABARG2*) subunit have been found in sporadic and familial idiopathic generalized epilepsies, especially in childhood absence epilepsy and juvenile myoclonic epilepsy [95]. However, *GABRA1A* is also a major causative gene for heterogeneous epileptic encephalopathies, including Ohtahara syndrome, infantile spasms, Dravet syndrome-like phenotypes and myoclonic astatic epilepsy [95] (Fig. 1). Red flags for suspecting *GABRA1A* mutations are infantile-onset epilepsy (from 1 day to 15 months of age), prominent tonic-clonic and myoclonic seizures, generalized spike-and-wave activity and a photoparoxysmal response. Such features can occur both in patients with idiopathic epilepsies and in those with epileptic encephalopathy [95] (Table 1, Fig. 2). No clear genotype-phenotype correlation has emerged, although the phenotype appears to be similar within single families [95]. Interestingly, GABA-A receptor has also been demonstrated to be involved in Angelman syndrome, a complex neurodevelopmental disorder characterized by ataxia, cortical tremor, sociable behaviour, seizures and intellectual disability. Angelman syndrome is mostly caused by deletion of the maternally derived chromosome 15q11-q13 region, which includes not only the causative *UBE3A* gene, but also the beta(3)-alpha(5)-gamma(3) GABA(A) receptor subunit gene cluster; post-mortem cortical tissues exhibit an abnormal shift in GABA-A receptor subunits compared with healthy controls [96].

NMDA receptors

The ligand-gated NMDA receptor is another ion channel involved in neurodevelopmental disorders. The channel is composed of two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits. It mediates excitatory neurotransmission between neurons allowing inflow of cations [97]. Mutations affecting the NR2 subunits (i.e. *GRIN2A*, *GRIN2B*) appear to be especially detrimental for neurodevelopment. The phenotypical spectrum of *GRIN2A* mutations includes patients with isolated intellectual disability, idiopathic focal epilepsy or epileptic encephalopathies. Interestingly, language disorders are common and range from mild speech impairment with no seizures to the epilepsy aphasia spectrum (atypical rolandic epilepsy, continuous spikes and waves during slow-wave sleep and Landau-Kleffner-Syndrome) [98]. In a child with GRIN2A encephalopathy, the targeted approach with the NMDA receptor antagonist memantine has successfully reduced seizure frequency [99], yet this observation in a single case remains to be confirmed in additional cases. Gain-of-function *GRIN2B* mutations cause West syndrome, as well as childhood onset focal epilepsy in association with intellectual disability. Cognitive skills depend upon the degree of channel function impairment [100]. In adults, *GRIN2A* mutations have been anecdotally reported in patients with schizophrenia and *GRIN2B* mutations in Alzheimer disease [101], yet such findings need to be confirmed in larger case series..

Conclusion

The clinical spectrum of genetic brain channelopathies ranges from life-threatening infantile-onset epileptic encephalopathies to mild adult-onset epilepsies. Epilepsy is the archetypical neurological phenotype with an extremely heterogeneous and variable presentation throughout life. In most cases, seizures are only part of complex encephalopathic phenotypes with widespread neurological signs often with a progressive course, attributable to the dysfunction of ion channels over the whole central nervous system, including the cerebral cortex and the cerebellum.

Technological advances currently allow extensive screening in single patients with suspected genetic epilepsy using gene panel analyses or exome sequencing. Despite this, the clinician's assessment remains of utmost importance. Recognizing the prominent phenotypical traits of brain channelopathies is essential to best employ molecular analyses. To identify single pathogenic variants may in turn guide the clinician in designing a tailored treatment. Understanding the spectrum of brain channelopathies may also prompt the adult neurologist to perform molecular investigations in patients who could not benefit from modern diagnostic technologies in their childhood.

Still the genetic diagnosis should be followed by the recognition of the potentially changing neurological phenotype at different ages, to provide better care not only in the paediatric setting but also for adult patients and their caregivers, especially in the delicate transition of care of people with epilepsy.

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