Orsini *et al*. *J Transl Genet Genom* 2018;2:16
DOI: 10.20517/jtgg.2018.14

Journal of Translational Genetics and Genomics

Review

Open Access

Personalized medicine in epilepsy patients

Alessandro Orsini[1], Mariagrazia Esposito[1], Daniele Perna[1], Alice Bonuccelli[1], Diego Peroni[2], Pasquale Striano[3]

[1]Pediatric Neurology Unit, "A.O.U. Pisana", University Hospital of Pisa, Pisa 56126, Italy.
[2]Pediatric Department, "A.O.U. Pisana", University Hospital of Pisa, Pisa 56126, Italy.
[3]Pediatric Neurology and Muscular Diseases Unit, DINOGMI-Department Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health University of Genoa, "G. Gaslini" Institute, Genova 16100, Italy.

Correspondence to: Dr. Mariagrazia Esposito, Pediatric Neurology Unit, "A.O.U. Pisana", University Hospital of Pisa, Pisa 56126, Italy. E-mail: maryagrazya@gmail.com; Dr. Daniele Perna, Pediatric Neurology Unit, "A.O.U. Pisana", University Hospital of Pisa, Pisa 56126, Italy. E-mail: daniele_perna@hotmail.it

How to cite this article: Orsini A, Esposito M, Perna D, Bonuccelli A, Peroni D, Striano P. Personalized medicine in epilepsy patients. *J Transl Genet Genom* 2018;2:16. https://doi.org/10.20517/jtgg.2018.14

Received: 20 Jun 2018 **First Decision:** 16 Aug 2018 **Revised:** 26 Sep 2018 **Accepted:** 26 Sep 2018 **Published:** 25 Oct 2018

Science Editor: Sheng-Ying Qin **Copy Editor:** Cui Yu **Production Editor:** Zhong-Yu Guo

Abstract

The large number of different syndromes and seizure types together with an interindividual variable response to antiepileptic drugs (AEDs) make the treatment of epilepsy challenging. Fortunately, the last few years have been characterized by a huge interest in epilepsy genetics and two methods, genome-wide analyses and next-generation sequencing, have definitely given the possibility to write a new chapter in the book of treatment of epilepsy, the chapter on precision medicine. Epilepsy offers a good opportunity for the personalization of therapy if we consider that at least one third of epileptic patients do not achieve complete seizure control with the currently available pharmacological treatments, treatment is still often empirical and precise therapy, based on the pathogenesis and the mechanism of each AED is not generally possible because this mechanism often remains incompletely known. In addition, new drugs are often not targeted but developed using *in vivo* seizure models, to be potentially used by the largest number of patients. This method leads to a therapy aimed at treating the symptoms and the seizures rather than the single pathogenic mechanism of each seizure type or syndrome. In this narrative review, we summarize the established evidence regarding pharmacogenomics in epilepsy and discuss the basis of precision medicine.

Keywords: Precision medicine, epilepsy treatment, antiepileptic drugs, next generation sequencing, pharmacogenomics in epilepsy

INTRODUCTION

Epilepsy is a medical condition defined by recurrent, or likely recurrent, seizures due to excessive electrical discharges in a group of brain cells[1]. Nowadays, treatment is limited to a wide range of antiepileptic drugs

(AEDs) with different mechanisms of action[2], which can only provide control of symptoms (seizures). It is ineffective in a large percentage of patients and can sometimes also worsen seizures or cause adverse reactions[3]. The heterogeneous etiology of epilepsy, the large number of different syndromes and seizure types, together with an individually variable response to AEDs, make the treatment of this condition still challenging[4,5]. Moreover, adverse drug effects can be severe and life-threatening and some AEDs can even worsen seizure control and induce new seizure types[6]. It is now well established that genetic factors are the explication of the interindividual variability in the response to AEDs[5]; different genes can be mutated thus affecting drug pharmacokinetics, drug pharmacodynamics or causing epilepsy itself. In addition, studies have shown that epigenetic mechanisms are involved in brain modifications due to epilepsy[7]. The term precision medicine aims to describe a personalization of treatments that ideally have to be targeted towards the precise molecular pathogenesis of disease[8]. Perhaps, the best realization of precision medicine is, to date, achieved in oncology specialties, which is called cancer precision medicine, a Barack Obama initiative in terms of funding. Epilepsy offers a good and challenging opportunity for the personalization of treatments for different reasons: it affects ~1% of worldwide populations at the age of 20 years and 3% at the age of 75 years[9], many patients are still not seizure-free or have adverse drug reactions, and the genetic bases of many epileptic syndromes are well studied nowadays while new genes are discovered every day.

To write this manuscript, a literature search was conducted through the PubMed database using the terms "epilepsy", "pharmacogenomics", "antiepileptic drugs", "pharmacogenetics" and "diagnostic sequencing" from 1997 to 2018. Additional information was found in the reference lists of selected articles.

Pharmacogenomics in epilepsy

Genetic mutation can alter response to AEDs at both pharmacokinetic (e.g., polymorphism in gene involved in drug metabolism) and pharmacodynamic level (e.g., polymorphism in brain AED targets, such as ion channels). Other mechanisms involved are mutations in genes causing epilepsy or the modification of the expression of enzymes and other molecules involved in the pathogenesis of pharmacoresistance or adverse drug reactions[10,11]. Pharmacogenomics is the science that studies how these genetic differences affect drug response both in terms of efficacy and susceptibility to adverse drug reactions[11]. It is in the last two decades that advances in genetic testing have led to a systematic search for gene variations that could predict drug response and ultimately improve the efficacy and safety of epilepsy therapies. As we already know, adverse drug effects can be severe and life-threatening and some AEDs can even worsen seizure control and induce new seizure types[6].

Genetic influences on AED metabolism

It is now well established that the clearance of most AEDs is linked to cytochrome P450 (CYP) enzymes activity. Polymorphisms of the gene encoding CYP enzymes can alter their activity, thus affecting serum AED concentrations and lead to drug toxicity[12] [Table 1]. A good example is phenytoin (first generation AED) which is metabolized primarily by *CYP2C9* and also by *CYP2C1*. Some individuals have *CYP2C9* polymorphisms, which cause a reduced activity of the enzyme thus leading to low phenytoin clearance, higher serum phenytoin concentrations and a greater risk of central nervous system adverse effects. *CYP2C9*2* (rs1799853) and *CYP2C9*3* [rs1057910(C)] are the best documented of these polymorphisms[13,14]. To the best of our knowledge, pre-treatment testing for *CYP2C9* variants is not considered as routine practice in any center. In our opinion, the best practice remains the clinical monitoring of signs of toxicity and of serum drug levels and it is also important to consider drug interactions if patients are taking other AEDs[15].

Another AED that has shown reduction of clearance due to genetic polymorphisms is phenobarbital (first generation AED). The enzyme involved is *CYP2C19*, with a difference of up to about 20%-50% in the reduction of clearance[16]. To the best of our knowledge, there is no evidence that genetic testing improves the outcome of phenobarbital therapy compared with clinical observation and monitoring of serum drug concentration[17]. A Japanese study showed that *CYP2C19* and *CYP3A5* polymorphisms are involved in the

Table 1. Genetic influences on AED metabolism

CYP	Effects	Reference
Reduced activity of *CYP2C9*(2-3)	Higher serum phenytoin concentration	[13,14]
Reduced activity of *CYP2C9*, *CYP2A6*, *CYP2B6* and UGT/genes enzymes	Valproato-related acid-induced liver damage	[19-22]
Reduced activity of *CYP2C19*	Higher serum phenobarbital and clobazam concentrations Zonisamide in Japanese p	[16-18]

AED: antiepileptic drug; UGT: uridine diphosphate glucuronosyltransferase

metabolism of zonisamide (second generation AED) leading to a reduction of clearance up to 16%-30%[18]. The clinical relevance of these changes is still to be clarified. In addition, drug interactions can increase zonisamide clearance, thus reducing the effects of the genetics variants.

Valproic acid (VPA) (first generation AED) is an AED that can cause severe adverse effects including severe hyperammonemia and non-alcoholic fatty liver disease. Liver damage due to VPA has been associated with the formation of the toxic 4-ene metabolite mediated by *CYP2C9*[19]. It has been shown that genetic testing for *CYP2C9* variant and subsequent different treatments significantly reduced VPA misdosing and hyperammonemia in a controlled trial[20]. A recent study showed that the content of 4-ene-VPA had no direct correlation with the incidence of liver dysfunction. In addition, VPA metabolism is also influenced by the polymorphism of *ACSM2A*, which can lead to higher levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) compared with wild-type subjects, however, the mutations had no effect on the VPA-related liver damage[21].

Finally, VPA metabolism is also influenced by genetically determined variation of uridine diphosphate glucuronosyltransferase (UGT) enzymes. A study conducted on a pediatric cohort showed that -161C > T single nucleotide polymorphism in *UGT2B7* gene led to significant differences in plasma VPA concentrations. Patients with the CC genotype had lower adjusted plasma VPA concentrations than those with CT or TT genotype (P = 0.028)[22]. Lamotrigine (second generation AED) is eliminated almost entirely by glucuronidation. An old study conducted in a small number of patients with Gilbert syndrome found that lamotrigine clearance was lower in these patients than in healthy control[23]. The clinical impact of this difference is still unknown. Other studies showed that *UGT1A4* genetic polymorphisms also influence lamotrigine clearance, such as -219C > T/-163G > A mutations in the 5'-upstream regions of the *UGT1A4* gene, which significantly increases lamotrigine (LTG) serum concentrations. However, other factors may play an important role in lamotrigine metabolism such as age, body weight and interaction with VPA[24,25].

Another second-generation AED, retigabine, is also metabolized by N-glucuronidation and N-acetylation, but its clearance has been found to be unaffected in Gilbert's syndrome although arylamine N-acetyltransferase-2 acetylator status did influence the disposition of the weakly active metabolite N-acetyl-retigabine[26]. There is no evidence of any benefit of dose adjustments for genetic polymorphisms[27].

Pharmacoresistance

It is well established that at least one third of epileptic patients do not achieve complete seizure control with currently available pharmacological treatments (AED)[28]. The cause of pharmacoresistance, is still not totally understood[29], but it has been shown that several ATP-dependent transport proteins are involved in drug resistance. Drug transporters actively eliminate toxins from the cells, including many drugs. One of the most studied transporters is P-glycoprotein (P-gp), encoded by the *ABCB1* gene[30]. In the brain, P-gp is expressed in astrocytes, endothelial cells and neurons, and there is evidence that its overexpression in epileptogenic tissue can be involved in pharmacoresistance to AEDs[31]. Several studies have shown that *ABCB1* gene variants are involved in the response to treatment in epilepsy patients. A retrospective case-control study of C3435T variants reported that patients with pharmacoresistant epilepsy were more likely to have the CC genotype than the TT genotype (27.5% and 19.5%, respectively) compared with AED responders

Table 2. Adverse drug reaction

HLA allele	Drug effect
HLA-B*15:02 and HLA-A*31:0	Carbamazepine
HLA-B*57:01	Abacavir
HLA-B*13:0	Dapsone
HLA-B*58:0	Allopurinol
HLA-B*15:02	Treatment with carbamazepine: SJS/TEN among patients of Han Chinese people (and phenytoine, oxcarbazepine, lamotrigine)
HLA-B* 31:01	Carbamazepine-induced hypersensitivity reactions, ranging from maculopapular exanthema, SJS/TEN to drug reaction with eosinophilia and systemic symptoms (DRESS) common both in Europeans and Orientals
HLA-B*15:02 (HLA-B75), HLAB*15:08, HLA-B*15:11, HLA-B*15:1	Carbamazepine-induced SJS/TEN

HLA: human leukocyte antigen; SJS/TEN: Stevens-Johnson syndrome and toxic epidermal necrolysis

(15.7% CC and 29.6% TT)[32]. Subsequently, other studies were made but were inconclusive[33,34]. In fact, two meta-analyses of these studies revealed no significant association between resistance to AEDs and the C3435T genotype[33,35]. Most recent studies continue to provide evidence of significant associations between drug resistance and *ABCB1* 3435 genotypes[36]. In addition, the results of a recent meta-analysis indicates that *ABCB1* C3435T polymorphism, especially TT genotype, plays an important role in refractory epilepsy; the authors suggest that genetic screening of this genotype, before starting the treatment, may be useful to predict AED response[37]. Studies of gene variants for other transporter proteins such as multidrugresistance-associated protein 2 (MRP2)/*ABCC2* failed to provide evidence for a clinical impact of these tests in epilepsy therapy[38,39]. A recent meta-analysis of studies on the expression and cellular distribution of MRP1 suggest that MRP1 is overexpressed in both neurons and astrocytes of patients with drug resistant epilepsy and that its inhibition may lead to treatment response due to increased local drug availability[40]. Many AEDs exert their pharmacological effects, at least in part, by blocking voltage-dependent sodium channels. Polymorphisms in the genes coding for these channels have been studied to investigate their relationship with drug resistance. Many studies[41,42] have suggested that *SCN1A* polymorphisms influence the response to sodium channel blocking AEDs. However, other studies did not confirm this association[43,44]. In fact, some patients with Dravet syndrome show seizure aggravation after sodium channel blockers intake[45]. However, it has been shown that lamotrigine can improve seizure control in some of these patients[46]. This conflicting results show how useful improvements in the field of precision medicine in epilepsy will be. Studies on other drug targets such as the GABA-A receptor[47], the *KCNT1* potassium channel[48] and the synaptic vesicle proteins SV2A, SV2B and SV2C[49], did not show any significant association. However, a recent Chinese study showed an association between some single-nucleotide polymorphisms of *KCNJ10* gene and anti-epileptic drug resistance[50]. In conclusion, to date, we still do not totally understand the real contribution of polymorphisms of AED target genes due to a lack of studies to evaluate the contribution of other factors to the individual variability of responses[51].

Adverse drug reaction

A link between genetic polymorphisms and the risk of side effects is well established. In particular, certain human leukocyte antigen (HLA) alleles are associated with an increased risk of idiosyncratic adverse drug reactions[52] [Table 2]. There is a special link between different types of drug and different alleles, like HLA-B*15:02 and HLA-A*31:01 for carbamazepine (first generation AED), HLA-B*57:01 for abacavir, HLA-B*13:01 for dapsone and HLA-B*58:01 for allopurinol.

There is evidence that in Han Chinese, Thai, and Malaysian populations the presence of HLA-B*15:02 is a genetic marker of risk for Stevens-Johnson syndrome (SJS) induced by carbamazepine, probably due to the activation of cytotoxic T-lymphocytes which is mediated by this allele[53,54]. A study showed that there is a significant decrease of carbamazepine-induced SJS-toxic epidermal necrolysis (TEN) if the subjects carrying

the HLA-B*1502 allele were previously identified and carbamazepine was thus avoided as a therapy[55]. The frequency of this allele in the specific population is in the order of 1%-8% in residents of China and most South Asian countries[52], with peaks as high as 15%-21% among Indonesians and 34% among Filipinos[56], while instead the frequency of the HLA-B*15:02 allele is very low (< 0.5%) in people of European, or North East Asian (Korean and Japanese) ancestry[57]. For these reasons regulatory agencies and guidelines (like the Clinical Pharmacogenetics Implementation Consortium Guidelines for HLA-B genotype and carbamazepine dosing) recommend that patients from Han Chinese and other South Asian ethnic groups be routinely genotyped for HLA-B*15:02 before starting treatment with carbamazepine, and that carbamazepine be avoided if possible in carriers of the allele[56,58]. The HLA-B*15:02 allele has also been associated with an increased risk of SJS and TEN after therapy with other AEDs, including phenytoin (first generation AED) and, to a lesser extent, lamotrigine[59], and oxcarbazepine (second generation AED)[60]. In fact, these AEDs have an aromatic ring just as carbamazepine (CBZ) does.

In addition, another allele, the HLA-A*31:01 has been linked with increased risk of carbamazepine-induced hypersensitivity reactions, such as maculopapular exanthema, SJS/TEN and also drug reaction with eosinophilia and systemic symptoms (DRESS)[61,62]. HLA-A*31:01 is frequent in many ethnic groups, both in Europeans and Orientals[63]. A recent meta-analysis confirmed a significant association of HLA-A*31:01 with carbamazepine-induced DRESS but a weaker association with CBZ-SJS/TEN, thus suggesting that HLA-A*31:01 is a genetic predictor for CBZ-DRESS but not for CBZ-SJS/TEN[64]. Studies have been made to find if, apart from a clinical benefit, genotyping for HLA-A*31:01, which reduces the incidence of cutaneous adverse drug reactions, could be economically convenient and the results show that this routine practice would be cost-effective[65].

The HLA-B*15:02 allele belongs to the HLA-B75 serotype, and other alleles belonging to the same serotype, such as HLAB*15:08, HLA-B*15:11 and HLA-B*15:18, have been associated with an increased risk of carbamazepine-induced SJS/TEN[52]. By contrast, some HLA alleles have been reported to be potentially protective against the risk of carbamazepine-induced SJS/TEN, such as HLA-B*40:01, HLA-B*07:02, HLAB*58:01, HLA-A*33:03, HLA-B*4001, HLA-B*4601 and HLA-DRB1*03:01[66,67].

In conclusion, to date, there is limited evidence regarding the value of genotyping in predicting AED response. The best example of a useful pharmacogenetic variant in epilepsy is testing for HLAB*15:02 to prevent serious adverse cutaneous reactions in individuals from South Asian ethnic groups in whom initiation of carbamazepine therapy is considered. Unfortunately, there is no widely applicable genetic test to predict response to AED treatment in patients with the most common forms of epilepsy. However, we believe that genetic testing will help in preventing adverse drug reactions or to prescribe the correct dose of AED. Furthermore, it will help researchers better understand epilepsy genetics and approach new precision medicine.

Precision therapy

The treatment of epilepsy is still largely based on empirical science and the prescription of drugs for epileptic patients cannot be based on the mechanisms of action of these. The performance of a personalized therapy is limited by the broad clinical phenotypic spectrum and the underlying heterogeneous aetiology. However, recent scientific acquisitions about genetics mechanisms, studies of neuroimaging and epilepsy neurobiology are providing many indications about the choice between the drugs of the past or the newest ones, thus laying the foundations for a new era in the treatment of epilepsy, in which patients will benefit from therapies based on the etiological cause of diseases[68].

The newest AEDs offer many therapeutic advantages compared to traditional and older generation therapies, in fact they have a lower risk profile of side effects and have by far fewer drug interactions. Despite this,

treatment is still largely empirical and rational prescribing based on the mechanism of action in an individual patient is not generally possible. A fundamental problem is that the main mechanisms of action and biochemical effects of drugs are not yet known in depth or not completely clear. This is in part due to the fact that the exact molecular targets of current AEDs are largely unidentified. Therefore, drug discovery is not targeted and instead relies on developments using *in vivo* seizure models. Further, as a consequence of these models, the common antiepileptic therapies are limited to controlling the epileptic symptoms but not to preventing the epileptogenic events. It seems likely that we will need to understand epileptogenesis in order to devise novel therapeutic interventions. Accordingly, research is rather oriented towards the mechanisms of action and the complex molecular processes to which diseases are subjected[69].

Genetic confirmation through the use of specific molecular diagnostic techniques in epileptic syndrome can provide an important contribution in establishing a more precise prognosis and in the evaluation of recurrence of epileptic seizures[70,71].

Furthermore, it offers an excellent opportunity to obtain better information on targeted treatments and the development of targeted drugs. The impact of increased knowledge is of paramount importance in particular in patients with epileptic encephalopathies, a group of neurodevelopmental disorders characterized by marked epileptic activity associated with regression of neurological development[72,73].

Current drugs directly reduce neuronal excitability mainly by modulating ion channels and neurotransmitter receptors. Recent acquisitions have revealed further pathways that show different mechanisms such as synaptic vesicle traffic, mammalian target of rapamycin (mTOR) signaling, chromatin remodeling and transcription, thus offering new therapies[74,75].

The genetics of epilepsy is still very complex, mutations of different genes can cause the same syndrome or even mutations in a single gene (for example, *SCN1A*) can be associated with a wide range of phenotypes, ranging from feverish convulsions to severe epileptic encephalopathies[76].

It is also important to underline that there is a wide individual variability of response to antiepileptic treatment and the genetic differences between patients are most likely implicated in this variation [Table 3].

Drug use

On the basis of a particular form of epilepsy we can explain, in whole or in part, the answer, both positive and negative (paradoxical) to certain AEDs. For instance, the clinical picture of Dravet syndrome can be worsened by the use of carbamazepine and phenytoin, since the disease is caused by mutations in the sodium channel gene (*SCN1A*) and these drugs interfere on the mechanism of action mentioned blocking the channel[4,69,77]. In contrast, sodium channel blocking is considered the first choice therapy for the epileptic syndrome associated with mutations in *SCN8A* (another sodium channel gene) and *KCNQ2* genes[4,49].

LTG is a known blocker of the sodium channel and N-type calcium channels and its use has sparked controversy. Some works claimed it as a factor in exacerbation of seizures, therefore research has led to the avoidance of its use in patients with Dravet syndrome. On the other hand, other studies assert a positive effect in some patients with Dravet syndrome. This beneficial effect could be explained by the mechanism involving the cyclic-nucleotide channels activated by hyperpolarization processes[47,51].

At present, approved therapy for Dravet syndrome includes the use of three drugs in a polytherapy that are valproate, clobazam and often stiripentol. As regards stiripentol, this is the only drug used in Dravet syndrome for which an important randomized controlled trial has been performed (when combined with valproate and clobazam); but it is widely known that the use of stiripentol, valproate and clobazam can cause

Table 3. Precision therapy

Gene	Pathology	Therapy
SCN1A	Dravet Syndrome	Valproate, clobazam, stiripentol, fenfluramine Recommended avoidance carbamazepine and phenytoin Controversial recommendations: lamotrigine
SCN8A E KCNQ2	From benign familial seizures to severe form of epileptic encephalopathy early onset	Carbamazepine and phenytoin
KCNQ2-5		Retigabine
GRIN2A	Early onset epileptic encephalopathy	Memantine
KCNT1	Focal epileptic seizures	Quinidine
POLG-epilepsies		Recommended avoidance Valproate
EPHX1	Kosovan people of Albanian ethnicity and Chinese people with epilepsy	Affected carbamazepine pharmacokinetic
SCN1A, *ABCC2*, *UGT2B7*	Han Chinese people with epilepsy	Affected maintenance dose of oxcarbazepine
Dysplasia, tuber growth and epileptic symptoms in tuberosis sclerosis hemimegalencephaly		Rapamycine (sirolimus)
DEPD5	Familial focal epilepsy with variable foci, autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy, rolandic epilepsy and other non-lesional focal childhood epilepsies and focal epilepsy associated with focal cortical dysplasia, both familial and sporadic	Rapamycine (sirolimus)
GATOR1	Focal epilepsy with cortical malformation	m-TOR inhibitors
Prickle mutations epilepsy		Inhibitors of USP9X
Glut1 deficiency syndrome and mutations in *SLC2A1*		Use of ketogenic diet
ALDH7A	Vit. B6-dependent epilepsy	Pyridoxine (vit. B6)
Resistant epilepsy, Dravet syndrome		Cannabidiol
Epileptic spasms in infancy		Steroids or ACTH and vigabatrin
KCN1A	Episodic ataxia type 1	Almorexant, ketogenic diet
SCN8A, SCN1A SCN2A	Epileptic encephalopathy	Low evidences about Na-channels blockers: amiodarone, bepridil, aprindine, cibenzolin, riluzole
KCNA2	Early infantile epileptic encephalopathy	4-aminopyrimidine and acetazolamide
CACNA1A	Infantile spasms, West syndrome	Ethosuximide
HCN1	Early infantile epileptic encephalopathy	Ivabradine, propofol, isoflurane, ketamine, lamotrigine, gabapentin
CHRNA4, CHRNB2 (nAChR)	Epileptic encephalopathy	nAChR antagonists

m-TOR: mammalian target of rapamycin; USP9X: ubiquitin-specific peptidase 9 X-linked; ACTH: Adrenocorticotropic Hormone; nAChRs: nicotinic acetylcholine receptors

serious side effects and, as is well known, it is capable of reducing the number of critical episodes but not completely eliminating them[77].

New and effective treatment strategies with possibly novel mechanisms are therefore needed.

Many studies confirm the efficacy of fenfluramine in Dravet syndrome[78,79]. This drug was initially developed as an appetite suppressant, but withdrawn from the market due to serious adverse effects, including cardiac and pulmonary problems such as valvular heart disease and pulmonary hypertension[80,81]. Fenfluramine has the ability to act on the serotoninergic cascade[82], but unfortunately the specific mechanisms by which it carries out its anti-epileptic actions still need to be discovered. More recent works affirm that fenfluramine significantly reduced epileptiform discharges in *SCN1A* knock-out morphants[83,84].

Retigabine (or ezogabine) (third generation AED), most often used in adult patients, is a drug that primarily acts as a positive allosteric modulator of *KCNQ2-5* ion channels (Kv7.2-7.5) and is the first drug used to treat epilepsy, which exploits its action on the potassium channels of neuronal cells[47]. *In vitro* studies show that the most potent action of this drug is on the *KCNQ2/3* heteromeric channels, which has been closely related to numerous forms of epileptic disorders from benign familial seizures to a severe form of epileptic encepha-

lopathy early onset[47]. Recent *in vitro* experiments have shown that retigabine opens Kv7 potassium channels and restores normal channel function in *KCNQ2*-related encephalopathy mutations[51].

Regarding the treatment of *GRIN2A*-related epileptic disorder, new strategies are based on the use of N-methyl-D-aspartate (NMDA) receptor antagonists[57]: memantine, an NMDA receptor antagonist approved by the Food and Drug Administration, has shown the ability to reduce the frequency and onset of seizures in some types of encephalopathies affecting children defined early-onset epileptic encephalopathy, associated with a *de novo* missense mutation in *GRIN2A* (p.Leu812Met). However, the same drug was not effective in another case-report in which the authors demonstrated a different mutation (p.Asn615Lys) in the same gene, but with a completely different effect on the function of the protein[85].

Quinidine, a well-known anti-arrhythmic drug, has been used to restore *in vitro* the hyperactivity of the *KCNT1* mutant potassium channel in Xenopus oocytes[86]. A recent clinical case presented a child in whom oral administration of this drug led to an improvement in epilepsy and psychomotor skills which he suffered from because of focal epileptic seizures due to a lack of the protein product of *KCNT1*[87]. However, the same drug had no efficacy in another patient with *KCNT1* mutation and with severe secondarily generalized focal seizures. Therefore, we must use a great deal of attention and experience, in using quinidine, in patients with such genetic dysfunction[88]. The serious side effects on the liver of patients using valproate and presenting a *POLG* gene mutation are well known[89].

Some papers have shown a strong correlation between the genetic polymorphisms that affect microsomal epoxide hydrolase (*EPHX1*) gene and pharmacokinetics of carbamazepine in Chinese patients suffering from some forms of epilepsy and in Kosovan people of Albanian ethnicity with epilepsy[90].

A study demonstrated that in patients with *SCN1A*, *ABCC2* and *UGT2B7* genetic polymorphisms there is the possibility of making important changes to oxcarbazepine maintenance doses[91].

In an Indian population the genetic contribution of *CYP1A1* alleles on treatment outcome in people with epilepsy was studied. In particular, it has been demonstrated, through a study carried out on a population of Indian women with epilepsy, that the mutation in the variant rs2606345, which consists in a reduction of the *CYP1A1* expression, determines a lack of response to the first line treatment with most used AEDs[92,93].

Rapamycin (sirolimus) has been shown to decrease cortical dysplasia and tuber growth in patients with tuberosis sclerosis, also decreasing epileptic symptoms; moreover, the same drug is useful in patients with hemimegalencephaly. One possible explanation is that sirolimus blocks the mTOR complex, whose overexpression causes dysplasia in various organs and the formation of glial bands, subependymal nodules, tumors during both the fetal phase and subsequent central nervouse system development[2]. Another clinical trial was performed to understand the effects of everolimus (a derivative of sirolimus) on subependymal giant cell astrocytoma growth and showed a sustained effect on tumor reduction over ≥ 5 years of treatment, with no safety concerns[94].

Very recently we learned that some forms of epilepsy listed below are associated with Dishevelled, Egl-10 and Pleckstrin domain containing protein 5 (DEPDC5) loss-of-function mutations, including autosomal dominant nocturnal frontal lobe epilepsy, familial focal epilepsy with variable foci, familial temporal lobe epilepsy, rolandic epilepsy and other non-lesional focal childhood epilepsies, and focal epilepsy associated with focal cortical dysplasia, both familial and sporadic. It has recently been demonstrated that mutations of DEPDC5 are associated with increased production activity of the mTOR signal cascade factors, because of the capability of DEPDC5 to reduce the mTOR activity. In global DEPDC5 knockout rats, in which the therapy was performed during the prenatal period, with rescued growth delay and embryonic lethality,

prevented enhanced cell size and dysmorphism of neurons[95]. Numerous studies show that the reduction of the mTOR signaling pathway is certainly a basic mechanism underlying the pathophysiology of epilepsy in rodents and humans[96].

GATOR1 complex gene mutations leading to mTORC1 pathway upregulation are closely related to the onset of focal epilepsy with cortical malformations. However, unfortunately, there is not enough scientific evidence to be able to state that treatment with mTOR inhibitors in patients with gene mutations affecting the *GATOR1* complex subunit is efficacious[97].

Mutations in the *PRICKLE* genes are associated with seizures in humans, zebrafish, mice, and flies, offering a seizure-suppression pathway that may be evolutionarily conserved. This path has never been studied in the past by the researchers who deal with antiepileptic therapy. The inhibition of ubiquitin-specific peptidase 9 X-linked (USP9X) can arrest *PRICKLE*-mediated seizures, so USP9X molecules may be evaluated as a new class of anti-seizure therapy[98].

There are various associations between specific genetic mutations and non-pharmacological and rational therapeutic decisions. The benefits of using a ketogenic diet in patients with Glut1 deficiency syndrome due to mutations in *SLC2A1* are widely known. The clinical spectrum of this condition is heterogeneous and includes a group of epileptic syndromes ranging from mild cases with no epilepsy to severe cases characterized by intractable epilepsy, infantile spasms and developmental delay. The treatment of first choice to resolve the symptoms due to neuroglycopenia consists in providing an alternative fuel to the brain through the ketones; this may be achieved through the use of a ketogenic diet[99]. It is of fundamental importance to start a ketogenic diet as early as possible, and therefore to make an early diagnosis to provide brain nourishment and control seizures[100]. However, the benefits on neurodevelopment seem controversial[101].

Biallelic mutations of the *ALDH7A1* gene cause a deficit of antiquitin and these mutations underlie pyridoxine (vitamin B6)-dependent epilepsy. The seizures are due to the fact that the lack of antiquininit is determined to accumulate 1-piperideine-6-carboxylate condenses with pyridoxal 5'-phosphate and inactivates this enzyme cofactor, essential component for the metabolism of the central nervous system and in specific neurotransmitters. The simple therapy using pyridoxine in most cases can lead to full control of convulsive episodes. *ALDH7A1* analysis of gene could also be used for prenatal diagnosis of pyridoxine-dependent epilepsy[102].

Cannabis sativa was the first plant cultivated by humans for purposes other than food or other useful purposes. For thousands of years, extracts of the plant have been used for a variety of therapeutic conditions, including the treatment of epilepsy. In recent times, with the power of the new social media, the general population have been more and more interested in and approached the topics concerning the use of cannabis-based therapies and in particular their effectiveness as a therapy in drug-resistant epilepsy, demonstrating significant benefits for the therapeutic indication. The research has also been very much addressed in its use for a severe epileptic encephalopathy of childhood called Dravet syndrome. Given the low number of studies and research on the use of cannabidiol as a drug for the therapy of variable symptoms including epileptic ones, recently the research has been oriented with more attention in this regard. For example, some children were recruited to whom cannabidiol was administered in particular formulations, a botanically-derived pharmaceutical, with compassionate use programs and were placed in an open-label trial[103,104].

In 2017 the results of a double-blind, placebo-controlled trial of cannabidiol in children with Dravet syndrome were published. The percentage of patients who had a greater than 50% reduction in convulsive seizure frequency was 43% with cannabidiol and 27% with placebo (OR 2.00, 95% CI 0.93-4.30, $P = 0.08$). These results

have been much needed to meet the high expectations regarding cannabis therapies for epilepsies, and this trial will serve as a model for future studies, much more specific in particular in rare diseases[105].

One therapy that must be mentioned is that of infantile spasms. This condition requires a specific therapy which should be carried out as early as possible to allow an adequate response to the therapy and avoid, as often happens, some cognitive sequelaes that can be determined if treatment is started too late. The two best-established therapies are hormonal treatments (steroids or adrenocorticotropic hormone) and vigabatrin (second generation AED); however, little international consensus exists on which treatment to use first. In 2017 O'Callaghan *et al*.[106] published a work that reported the results of an International Collaborative Infantile Spasms Study, the most important open-label randomized trial for the treatment of infantile spasms carried out so far. For this multinational trial, 102 hospitals in five countries screened 766 infants over a 7-year period, 377 of whom were recruited to the study. The children were randomly divided into either the group in which a hormonal monotherapy was administered, or in the one in which a therapeutic association was combined with the AEDs. The patients were free of spasms between days 14 and 42. This outcome was achieved in 72% of infants in the combined treatment arm compared with 57% of those on hormonal therapy alone. The response to therapy was better in patients who did not have a well-established cause for their disease, without an identifiable etiology[106].

The different genetic polymorphisms can determine variations both in the pharmacokinetic field (absorption, distribution, transport, metabolism, elimination) and in those of the pharmacodynamics (action sites, *etc*.).

The genetic test is the background of an individual variation in the response to antiepileptic treatment, in terms of efficacy and adverse reactions.

The *KCNA1* mutations are associated with episodic ataxia type 1[107,108] and homozygous Kv1.1 knockout mice have disrupted sleep, and seizures peak during times of light[109]. Almorexant, a dual orexin receptor antagonist used in sleeping disorders, improves sleep and reduces seizure severity, suggesting that it may be useful for patients with mutations in *KCNA1*[110]. Treatment of homozygous Kv1.1 knockout mice with a ketogenic diet also reduces seizure frequency and has been shown to successfully extend life span[100]. Finally, homozygous Kv1.1 knockout mice with partial genetic ablation of NaV1.2 exhibit reduced duration of spontaneous seizures, and a significant improvement of survival rates argues that blockers of this Na^+ channel may have some treatment value[111].

Heterozygous mutations in *SCN8A* are associated with an epileptic encephalopathy characterized by developmental delay, seizure onset within the first 18 months of life, and intractable epilepsy. These patients have multiple seizure types, including infantile spasms, generalized tonic-clonic seizures, absences, and focal seizures[112]. Mirroring the situation with *SCN1A* and *SCN2A*, where there are both mild and severe phenotypes, very recently there were two reports of familial benign infantile seizures, without cognitive impairment, and some with paroxysmal dyskinesias with missense variants in *SCN8A*[113,114]. The research provides a number of potential targeted therapeutic options. In particular, targeting the increased persistent Na^+ current makes sense. Significantly, GS967, a specific blocker of persistent Na^+ current, extends the survival of the NaV1.6 (N1768D/+) mouse[115]. Riluzole, a drug known for its mild efficacy in the treatment of amyotrophic lateral sclerosis, has proved to be an important therapeutic possibility, thanks to its capability as Na^+ current blocker. Riluzole is effective in blocking the early depolarization events seen in CA1 pyramidal neurons[116], but as yet there is no published evidence of its efficacy in the NaV1.6 (N1768D/+) mouse. Patel *et al*.[117] have also demonstrated that increased persistent current of Nav1.6 mutant channels can be preferentially reversed with cannabidiol.

A further mechanism involving ionic channels has been extensively studied, is the one concerned with blocking the Na^+/Ca^{2+} exchanger which is implicated in the disease mechanism[116].

It is known that some drugs capable of blocking the Na^+/Ca^{2+} exchanger (amiodarone[118], bepridil[119], aprindine[120] and cibenzoline[121]) are considered important therapeutic options also in epilepsies.

De novo mutations in *KCNA2* have been identified in cases of early infantile epileptic encephalopathy. In this pathology the onset of seizures is between 5 and 17 months, with a phenotypic spectrum including febrile and afebrile, hemiclonic, myoclonic, myoclonic-atonic, absence, focal dyscognitive, focal, and generalized seizures; mild to moderate intellectual disability; delayed speech development; severe ataxia[122]. The *KCNA2* spectrum also encompasses milder familial epilepsy[123]. Some treatment options have been taken into consideration. The 4-aminopyridine is an approved K^+ blocker already being trialed in patients carrying gain-of function mutations. Xie *et al*.[124] have tested a non-targeted approach and reported that the carbonic anhydrase inhibitor, acetazolamide, is capable of rescuing the motor incoordination in Pingu mice.

Early evidence supported the idea that *CACNA1A* mutations were associated with genetic generalized epilepsies[125,126]. Micro-deletions that encompass *CACNA1A* and a single truncating mutation have been associated with severe epileptic encephalopathies that include infantile spasms and West syndrome. *De novo* missense mutations have been convincingly shown to cause severe epileptic encephalopathies with seizure types that typically include focal, tonic, and tonic-clonic seizures, severe intellectual disability and motor impairment[127,128]. It is known that acetazolamide and 4-aminopyridine are able to decrease, in tottering mice, the high-power low-frequency oscillations, which are thought to be a marker of cortical excitability, so these drugs are evaluated as treatment options for episodic ataxia 2[129]. Spontaneous seizures in the *CACNA1A* knockout mouse can be abolished by knocking out *CACNA1G*[130]. This suggests that T-type Ca^{2+} channel blockers, including ethosuximide, may be good therapeutic options[131].

Numerous studies of literature on animal models have shown concrete evidence regarding the transcriptional changes of hyperpolarization-activated cyclic nucleotide-gate (HCN) channels in correlation with excitability, but there remains little evidence on the association between epilepsy and genetic change correlated to the mentioned channels. A study by Nava *et al*.[132] showed that HCN1 missense mutations were associated with the development of early infantile epileptic encephalopathy. In addition, these patients had symptoms associated with Dravet syndrome with intellectual impairment and autism. In gain-of-function disease, HCN1 blockers may be useful. Ivabradine is a use-dependent broad-spectrum blocker of HCN channels approved for use in angina pectoris. It is an important drug because it is well tolerated by most patients, however, its capacity is not known, nor is the timing to overcome the encephalic barrier[133]. The hypnotics propofol and ketamine, as well as the anesthetic isoflurane, are reported to inhibit HCN1 channels[134-136]. Finally, the AEDs, lamotrigine and gabapentin (second generation AED), have both been reported to enhance HCN currents[137,138], potentially benefiting in particular patients with loss-of-function mutations.

In patients with mutation of the receptor for nACh, even if the type of mutation has been known for a long time, numerous precision therapy options have not yet been found. Only carbamazepine proved to be useful in patients with nicotinic acetylcholine receptors mutations with approximately 70% showing remission on low doses. Molecular and cellular studies argue that drugs that block nAChR should be effective in disease caused by mutations in *CHRNA4*, *CHRNB2*, and *CHRNA2c*[139,140] [Table 4].

In conclusion, cost-effectiveness of precision medicine was considered in this review. An interesting and recent study investigating the cost-effectiveness of a whole exome sequencing (WES)-based gene panel (targeted WES) in patients with severe epilepsies of infancy found that early targeted WES had lower total

Table 4. Precision therapy: genetic influences and applied methods

Gene	Pathology	Therapy	Applied method	Genetic influences toxicity
		Valproato, clobazam, stiripentol, fenfluramine	*In vivo*	X
SCN1A	Dravet syndrome	Recommended avoidance carbamazepine and phenytoin	*In vivo*	X
		Controversial recommendations: lamotrigine	*In vivo*	X
SCN8A E KCNQ2	From benign familial seizures to severe form of epileptic encephalopathy early onset	Carbamazepine and phenytoin	*In vitro*	
KCNQ2-5		Retigabine	*In vitro*	
GRIN2A	Early onset epileptic encephalopathy	Memantine	*In vivo*	
KCNT1	Focal epileptic seizures	Quinidine	*In vivo*	
POLG-epilepsies		Recommended avoidance valproate	*In vivo*	X
EPHX1	Kosovan people of Albanian ethnicity and Chinese people with epilepsy	Affected carbamazepine pharmacokinetic	*In vivo*	X
SCN1A, *ABCC2*, *UGT2B7*	Han Chinese people with epilepsy	Affected maintenance dose of oxcarbazepine	*In vivo*	X
Dysplasia, tuber growth and epileptic symptoms in tuberosis sclerosis. Haemimegalencephaly.		Rapamycine (sirolimus)	*In vivo*	
DEPD5	Familial focal epilepsy with variable foci, autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy, rolandic epilepsy and other non-lesional focal childhood epilepsies and focal epilepsy associated with focal cortical dysplasia, both familial and sporadic	Rapamycine (sirolimus)	*In vivo*	
GATOR1	Focal epilepsy with cortical malformation	m-TOR inhibitors	*In vivo*	
PRICKLE mutations epilepsy		Inhibitors of USP9X	*In vivo*	
Glut1 deficiency syndrome and mutations in *SLC2A1*		Use of ketogenic diet	*In vivo*	
ALDH7A	Vit-B6 dependent epilepsy	Pyridoxine (vit-B6)	*In vivo*	
Resistant epilepsy, Dravet syndrome		Cannabidiol	*In vivo*	
Epileptic spasms in infancy		Steroids or ACTH and vigabatrin	*In vivo*	
KCN1A	Episodic ataxia type 1	Almorexant, ketogenic diet,	*In vitro*	
SCN8A SCN1A SCN2A	Epileptic encephalopathy	Low evidences about Na-channels blockers: amiodarone, bepridil, aprindine, cibenzolin, riluzole	*In vivo*	
KCNA2	Early infantile epileptic encephalopathy	4-aminopyrimidine and acetazolamide	*In vitro*	
CACNA1A	Infantile spasms, West syndrome	Ethosuximide	*In vitro*	
HCN1	Early infantile epileptic encephalopathy	Ivabradine, propofol, isoflurane, ketamine, lamotrigine, gabapentin	*In vivo*	
CHRNA4, *CHRNB2* (nAChR)	Epileptic encephalopathy	nAChR antagonists	*In vivo*	

USP9X: ubiquitin-specific peptidase 9 X-linked; ACTH: Adrenocorticotropic Hormone; nAChRs: nicotinic acetylcholine receptors

cost than a late WES. A diagnostic approach with early targeted WES and limited metabolic testing leaded to 7 additional diagnoses compared to investigation without targeted WES (46/86 *vs.* 39/86), with lower total cost ($455,597 USD *vs.* $661,103 USD) and lower cost per diagnosis ($9904 USD *vs.* $16,951 USD)[141]. Another study was conducted in a neurogenetic clinic of a tertiary hospital in Argentina and confirmed the effective WES-based approach[142]. Additional studies on cost-effectiveness in precision medicine in epilepsy are needed, as healthcare system demands better allocation of its limited resources, still pursuing the best possible outcome for patients.

CONCLUSION

Mechanisms underlying epilepsy are multiple and it is very difficult to realize "the gold standard" of AED. Precision medicine is the future for antiepileptic treatment and can bring a better outcome also for some kind of epilepsy syndrome that in the past had been considered quite intractable. For example, in a particular

type of epilepsy syndrome like Glut1 deficiency (chetogenic diet) or in *GRIN2A* mutations (memantine) or in tuberous sclerosis complex (rapamycin), precision medicine is already possible with good results. The future effort of the research must be to identify new drugs against specific pathogenic mechanisms, or a specific action of mutated proteins, up to a gene replacement therapy, and also the individual genetic polymorphism that could result in impaired effect of the conventional AEDs[143].

DECLARATIONS

Acknowledgments

We thank Wendy Doherty, native English speaker and English Lecturer at University of Pisa for her assistance in screen and correct our manuscript for English language.

Authors' contributions

Conceived the presented idea and planned this work, conceived the study and were in charge of overall direction and planning: Orsini A, Striano P

Investigate specific aspects of "precision" medicine and supervised the findings of this work: Orsini A, Perna D, Esposito M

Provided critical feedback and helped shape the research: Bonuccelli A, Striano P, Peroni D

Discussed the results and contributed to the final review: Orsini A, Esposito M, Perna D, Bonuccelli A, Peroni D, Striano P

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, et al. How long for epilepsy remission in the ILAE definition? Epilepsia 2017;58:1486-7.
2. Striano P, Zara F. Mutations in mTOR pathway linked to megalencephaly syndromes. Nat Rev Neurol 2012;8:542-4.
3. Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult epilepsy. Lancet 2006;367:1087-100.
4. Guerrini R. Epilepsy in children. Lancet 2006;367:499-524.
5. Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. Lancet Neurol 2011;10:446-56.
6. Striano P, Vari MS, Mazzocchetti C, Verrotti A, Zara F. Management of genetic epilepsies: from empirical treatment to precision medicine. Pharmacol Res 2016;107:426-9.
7. Iori V, Aronica E, Vezzani A. Epigenetic control of epileptogenesis by miR-146a. Oncotarget 2017;8:45040-1.
8. EpiPM Consortium. A roadmap for precision medicine in the epilepsies. Lancet Neurol 2015;14:1219-28.
9. Browne TR, Holmes GL. Handbook of Epilepsy. 4th ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

10. Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. Epilepsia 2009;50:1-23.
11. Walker LE, Mirza N, Yip VLM, Marson AG, Pirmohamed M. Personalized medicine approaches in epilepsy. J Intern Med 2015;277:218-34.
12. Lopez-Garcia MA, Feria-Romero IA, Fernando-Serrano H, Escalante-Santiago D, Grijalva I, et al. Genetic polymorphisms associated with antiepileptic metabolism. Front Biosci (Elite Ed) 2014;6:377-86.
13. Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther 2014;96:542-8.
14. Depondt C, Godard P, Espel RS, Da Cruz AL, Lienard P, et al. A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. Eur J Neurol 2011;18:1159-64.
15. Franco V, Perucca E. CYP2C9 polymorphisms and phenytoin metabolism: implications for adverse effects. Expert Opin Drug Metab Toxicol 2015;11:1269-79.
16. Goto S, Seo T, Murata T, Nakada N, Ueda N, et al. Population estimation of the effects of cytochrome P450 2C9 and 2C19 polymorphisms on phenobarbital clearance in Japanese. Ther Drug Monit 2007;29:118-21.
17. Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE commission on therapeutic strategies. Epilepsia 2008;49:1239-76.
18. Okada Y, Seo T, Ishitsu T, Wanibuchi A, Hashimoto N, et al. Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. Ther Drug Monit 2008;30:540-3.
19. Sadeque AJ, Fisher MB, Korzekwa KR, Gonzalez FJ, Rettie AE. Human CYP2C9 and CYP2A6 mediate formation of the hepatotoxin 4-ene-valproic acid. J Pharmacol Exp Ther 1997;283:698-703.
20. Bűdi T, Tóth K, Nagy A, Szever Z, Kiss Á, et al. Clinical significance of CYP2C9-status guided valproic acid therapy in children. Epilepsia 2015;56:849-55.
21. Wang C, Wang P, Yang LP, Pan J, Yang X, et al. Association of CYP2C9, CYP2A6, ACSM2A, and CPT1A gene polymorphisms with adverse effects of valproic acid in Chinese patients with epilepsy. Epilepsy Res 2017;132:64-9.
22. Inoue K, Suzuki E, Yazawa R, Yamamoto Y, Takahashi T, et al. Influence of uridine diphosphate glucuronosyltransferase 2B7 -161C > T polymorphism on the concentration of valproic acid in pediatric epilepsy patients. Ther Drug Monit 2014;36:406-9.
23. Posner J, Cohen AF, Land G, Winton C, Peck AW. The pharmacokinetics of lamotrigine (BW430C) in healthy subjects with unconjugated hyperbilirubinaemia (Gilbert's syndrome). Br J Clin Pharmacol 1989;28:117-20.
24. Wang Q, Liang M, Dong Y, Yun W, Qiu F, et al. Effects of UGT1A4 genetic polymorphisms on serum lamotrigine concentrations in Chinese children with epilepsy. Drug Metab Pharmacokinet 2015;30:209-13.
25. Chang Y, Yang LY, Zhang MC, Liu SY. Correlation of the UGT1A4 gene polymorphism with serum concentration and therapeutic efficacy of lamotrigine in Han Chinese of Northern China. Eur J Clin Pharmacol 2014;70:941-6.
26. Hermann R, Borlak J, Munzel U, Niebch G, Fuhr U, et al. The role of Gilbert's syndrome and frequent NAT2 slow acetylation polymorphisms in the pharmacokinetics of retigabine. Pharmacogenomics J 2006;6:211-9.
27. Tompson DJ, Crean CS. Clinical Pharmacokinetics of retigabine/ezogabine. Curr Clin Pharmacol 2013;8:319-31.
28. Moshé SL, Perucca E, Ryvlin P, Tomson T. Epilepsy: new advances. Lancet 2015;385:884-98.
29. Sisodiya SM, Marini C. Genetics of antiepileptic drug resistance. Curr Opin Neurol 2009;22:150-6.
30. Dallas S, Miller DS, Bendayan R. Multidrug resistance-associated proteins: expression and function in the central nervous system. Pharmacol Rev 2006;58:140-61.
31. Potschka H, Brodie MJ. Pharmacoresistance. Handb Clin Neurol 2012;108:741-57.
32. Siddiqui A, Kerb R, Weale ME, Brinkmann U, Smith A, et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. N Engl J Med 2003;348:1442-8.
33. Haerian BS, Lim KS, Mohamed EH, Tan HJ, Tan CT, et al. Lack of association of ABCB1 and PXR polymorphisms with response to treatment in epilepsy. Seizure 2011;20:387-94.
34. Manna I, Gambardella A, Labate A, Mumoli L, Ferlazzo E. Polymorphism of the multidrug resistance 1 gene MDR1/ABCB1 C3435T and response to antiepileptic drug treatment in temporal lobe epilepsy. Seizure 2015;24:124-6.
35. Bournissen FG, Moretti ME, Juurlink DN, Koren G, Walker M, et al. Polymorphism of the MDR1/ABCB1 C3435T drug-transporter and resistance to anticonvulsant drugs: a meta-analysis. Epilepsia 2009;50:898-903.
36. Keangpraphun T, Towanabut S, Chinvarun Y, Kijsanayotin P. Association of ABCB1 C3435T polymorphism with phenobarbital resistance in Thai patients with epilepsy. J Clin Pharm Ther 2015;40:315-9.
37. Chouchi M, Kaabachi W, Klaa H, Tizaoui K, Turki IB, et al. Relationship between ABCB1 3435TT genotype and antiepileptic drugs resistance in epilepsy: updated systematic review and meta-analysis. BMC Neurol 2017;17:32.
38. Kim DW, Lee SK, Chu K, Jang IJ, Yu KS, et al. Lack of association between ABCB1, ABCG2, and ABCC2 genetic polymorphisms and multidrug resistance in partial epilepsy. Epilepsy Res 2009;84:86-90.
39. Ufer M, Mosyagin I, Muhle H, Jacobsen T, Haenisch S, et al. Non-response to antiepileptic pharmacotherapy is associated with the ABCC2 -24C > T polymorphism in young and adult patients with epilepsy. Pharmacogenet Genomics 2009;19:353-62.
40. Sun Y, Luo X, Yang K, Sun X, Li X, et al. Neural overexpression of multidrug resistance-associated protein 1 and refractory epilepsy: a meta-analysis of nine studies. Int J Neurosci 2016;126:308-17.

41. Tate SK, Depondt C, Sisodiya SM, Cavalleri GL, Schorge S, et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. Proc Natl Acad Sci U S A 2005;102:5507-12.
42. Baghel R, Grover S, Kaur H, Jajodia A, Rawat C, et al. Evaluating the role of genetic variants on first-line antiepileptic drug response in North India: significance of SCN1A and GABRA1 gene variants in phenytoin monotherapy and its serum drug levels. CNS Neurosci Ther 2016;22:740-57.
43. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, et al. Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 2010;363:1801-11.
44. Haerian BS, Baum L, Kwan P, Tan HJ, Raymond AA, et al. SCN1A, SCN2A and SCN3A gene polymorphisms and responsiveness to antiepileptic drugs: a multicenter cohort study and meta-analysis. Pharmacogenomics 2013;14:1153-66.
45. Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329-36.
46. Dalic L, Mullen SA, Roulet Perez E, Scheffer I. Lamotrigine can be beneficial in patients with Dravet syndrome. Dev Med Child Neurol 2015;57:200-2.
47. Zhou BT, Zhou QH, Yin JY, Li GL, Qu J, et al. Effects of SCN1A and GABA receptor genetic polymorphisms on carbamazepine tolerability and efficacy in Chinese patients with partial seizures: 2-year longitudinal clinical follow-up. CNS Neurosci Ther 2012;18:566-72.
48. Qu J, Zhang Y, Yang ZQ, Mao XY, Zhou BT, et al. Gene-wide tagging study of the association between KCNT1 polymorphisms and the susceptibility and efficacy of genetic generalized epilepsy in Chinese population. CNS Neurosci Ther 2014;20:140-6.
49. Lynch JM, Tate SK, Kinirons P, Weale ME, Cavalleri GL, et al. No major role of common SV2A variation for predisposition or levetiracetam response in epilepsy. Epilepsy Res 2009;83:44-51.
50. Guo Y, Yan KP, Qu Q, Qu J, Chen ZG, et al. Common variants of KCNJ10 are associated with susceptibility and anti-epileptic drug resistance in Chinese genetic generalized epilepsies. PLoS One 2015;10:e0124896.
51. Piana C, Antunes Nde J, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. Expert Opin Drug Metab Toxicol 2014;10:341-58.
52. Cheng CY, Su SC, Chen CH, Chen WL, Deng ST, et al. HLA associations and clinical implications in T-Cell mediated drug hypersensitivity reactions: an updated review. J Immunol Res 2014;2014:565320.
53. Chung WH, Hung SI, Hong HS, Hsih MS, Yang LC, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature 2004;428:486.
54. Tangamornsuksan W, Chaiyakunapruk N, Somkrua R, Lohitnavy M, Tassaneeyakul W. Relationship between the HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. JAMA Dermatol 2013;149:1025-32.
55. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med 2011;364:1126-33.
56. Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia 2014;55:496-506.
57. Leckband SG, Kelsoe JR, Dunnenberger HM, George AL Jr, Tran E, et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clin Pharmacol Ther 2013;94:324-8.
58. Ferrell PB Jr, McLeod HL. Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. Pharmacogenomics 2008;9:1543-6.
59. Cheung YK, Cheng SH, Chan EJ, Lo SV, Ng MH, et al. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. Epilepsia 2013;54:1307-14.
60. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349-56.
61. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med 2011;364:1134-43.
62. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet 2010;20:1034-41.
63. Kaniwa N, Saito Y. The risk of cutaneous adverse reactions among patients with the HLA-A* 31:01 allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: a perspective review. Ther Adv Drug Saf 2013;4:246-53.
64. Genin E, Chen DP, Hung SI, Sekula P, Schumacher M, et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J 2014;14:281-8.
65. Plumpton CO, Yip VL, Alfirevic A, Marson AG, Pirmohamed M, et al. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia 2015;56:556-63.
66. Wang W, Hu FY, Wu XT, An DM, Yan B, et al. Genetic predictors of Stevens-Johnson syndrome and toxic epidermal necrolysis induced by aromatic antiepileptic drugs among the Chinese Han population. Epilepsy Behav 2014;37:16-9.
67. Wang Q, Sun S, Xie M, Zhao K, Li X, et al. Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: a meta-analysis. Epilepsy Res 2017;135:19-28.
68. Striano P. Epilepsy towards the next decade: new trends and hopes in epileptology. Cham: Springer; 2014.
69. Reid CA, Jackson GD, Berkovic SF, Petrou S. New therapeutic opportunities in epilepsy: a genetic perspective. Pharmacol Ther 2010;128:274-80.

70. Møller RS, Dahl HA, Helbig I. The contribution of next generation sequencing to epilepsy genetics. Expert Rev Mol Diagn 2015;15:1531-8.
71. Myers CT, Mefford HC. Advancing epilepsy genetics in the genomic era. Genome Med 2015;7:91.
72. Covanis A. Clinical management of epileptic encephalopathies of childhood and infancy. Expert Rev Neurother 2014;14:687-701.
73. Striano P, Striano S. New and investigational antiepileptic drugs. Expert Opin Investig Drugs 2009;18:1875-84.
74. Striano P, Striano S, Minetti C, Zara F. Refractory, life-threatening status epilepticus in a 3-year-old girl. Lancet Neurol 2008;7:278-84.
75. Striano P, de Jonghe P, Zara F. Genetic epileptic encephalopathies: is all written into the DNA? Epilepsia 2013;54:22-6.
76. Brunklaus A, Zuberi SM. Dravet syndrome-from epileptic encephalopathy to channelopathy. Epilepsia 2014;55:979-84.
77. Balestrini S, Sisodiya SM. Pharmacogenomics in epilepsy. Neurosci Lett 2018;667:27-39.
78. Ceulemans B, Schoonjans AS, Marchau F, Paelinck BP, Lagae L. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. Epilepsia 2016;57:e129-34.
79. Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia 2012;53:1131-9.
80. McCann UD, Seiden LS, Rubin LJ, Ricaurte GA. Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine. A systematic review of the evidence. JAMA 1997;278:666-72.
81. Dahl CF, Allen MR, Urie PM, Hopkins PN. Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. BMC Med 2008;6:34.
82. Fuller RW, Snoddy HD, Robertson DW. Mechanisms of effects of d-fenfluramine on brain serotonin metabolism in rats: uptake inhibition versus release. Pharmacol Biochem Behav 1988;30:715-21.
83. Dinday MT, Baraban SC. Large-scale phenotype-based antiepileptic drug screening in a zebrafish model of Dravet syndrome. eNeuro 2015; doi: 10.1523/ENEURO.0068-15.2015.
84. Zhang Y, Kecskés A, Copmans D, Langlois M, Crawford AD, et al. Pharmacological characterization of an antisense knockdown zebrafish model of Dravet syndrome: inhibition of epileptic seizures by the serotonin agonist fenfluramine. PLoS One 2015;10:e0125898.
85. Pierson TM, Yuan H, Marsh ED, Fuentes-Fajardo K, Adams DR, et al. GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine. Ann Clin Transl Neurol 2014;1:190-8.
86. Møller RS, Heron SE, Larsen LH, Lim CX, Ricos MG, et al. Mutations in KCNT1 cause a spectrum of focal epilepsies. Epilepsia 2015;56:e114-20.
87. Milligan CJ, Li M, Gazina EV, Heron SE, Nair U, et al. KCNT1 gain of function in 2 epilepsy phenotypes is reversed by quinidine. Ann Neurol 2014;75:581-90.
88. Mikati MA, Jiang YH, Carboni M, Shashi V, Petrovski S, et al. Quinidine in the treatment of KCNT1-positive epilepsies. Ann Neurol 2015;78:995-9.
89. Engelsen BA, Tzoulis C, Karlsen B, Lillebø A, Laegreid LM, et al. POLG1 mutations cause a syndromic epilepsy with occipital lobe predilection. Brain 2008;131:818-28.
90. Daci A, Beretta G, Vllasaliu D, Shala A, Govori V, et al. Polymorphic variants of SCN1A and EPHX1 influence plasma carbamazepine concentration, metabolism and pharmacoresistance in a population of Kosovar Albanian epileptic patients. PLoS One 2015;10:e0142408.
91. Ma CL, Wu XY, Jiao Z, Hong Z, Wu ZY, et al. SCN1A, ABCC2 and UGT2B7 gene polymorphisms in association with individualized oxcarbazepine therapy. Pharmacogenomics 2015;16:347-60.
92. Grover S, Talwar P, Gourie-Devi M, Gupta M, Bala K, et al. Genetic polymorphisms in sex hormone metabolizing genes and drug response in women with epilepsy. Pharmacogenomics 2010;11:1525-34.
93. Talwar P, Kanojia N, Mahendru S, Baghel R, Grover S, et al. Genetic contribution of CYP1A1 variant on treatment outcome in epilepsy patients: a functional and interethnic perspective. Pharmacogenomics J 2017;17:242-51.
94. Franz DN, Agricola K, Mays M, Tudor C, Care MM, et al. Everolimus for subependymal giant cell astrocytoma: 5-year final analysis. Ann Neurol 2015;78:929-38.
95. Marsan E, Ishida S, Schramm A, Weckhuysen S, Muraca G, et al. Depdc5 knockout rat: a novel model of mTORopathy. Neurobiol Dis 2016;89:180-9.
96. Galanopoulou AS, Gorter JA, Cepeda C. Finding a better drug for epilepsy: the mTOR pathway as an antiepileptogenic target. Epilepsia 2012;53:1119-30.
97. Scheffer IE, Heron SE, Regan BM, Mandelstam S, Crompton DE, et al. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. Ann Neurol 2014;75:782-7.
98. Paemka L, Mahajan VB, Ehaideb SN, Skeie JM, Tan MC, et al. Seizures are regulated by ubiquitin-specific peptidase 9 X-linked (USP9X), a de-ubiquitinase. PLoS Genet 2015;11:e1005022.
99. De Vivo DC, Leary L, Wang D. Glucose transporter 1 deficiency syndrome and other glycolytic defects. J Child Neurol 2002;17:3S15-23.
100. Simeone KA, Matthews SA, Rho JM, Simeone TA. Ketogenic diet treatment increases longevity inKcna1-null mice, a model of sudden unexpected death in epilepsy. Epilepsia 2016;57:e178-82.
101. De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: current state of the art. Seizure 2013;22:803-11.
102. Mills PB, Struys E, Jakobs C, Plecko B, Baxter P, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. Nat Med 2006;12:307-9.
103. Zuberi SM, Brunklaus A. Epilepsy in 2017: precision medicine drives epilepsy classification and therapy. Nat Rev Neurol 2018;14:67-8.

104. Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270-8.
105. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376:2011-20.
106. O'Callaghan FJ, Edwards SW, Alber FD, Hancock E, Johnson AL, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurol 2017;16:33-42.
107. Eunson LH, Rea R, Zuberi SM, Youroukos S, Panayiotopoulos CP, et al. Clinical, genetic, and expression studies of mutations in the potassium channel gene KCNA1 reveal new phenotypic variability. Ann Neurol 2000;48:647-56.
108. Rajakulendran S, Schorge S, Kullmann DM, Hanna MG. Episodic ataxia type 1: a neuronal potassium channelopathy. Neurotherapeutics 2007;4:258-66.
109. Wright S, Wallace E, Hwang Y, Maganti R. Seizure phenotypes, periodicity, and sleep-wake pattern of seizures in Kcna-1 null mice. Epilepsy Behav 2016;55:24-9.
110. Roundtree HM, Simeone TA, Johnson C, Matthews SA, Samson KK, et al. Orexin receptor antagonism improves sleep and reduces seizures in Kcna1-null mice. Sleep 2016;39:357-68.
111. Mishra V, Karumuri BK, Gautier NM, Liu R, Hutson TN, et al. Scn2a deletion improves survival and brain-heart dynamics in the Kcna1-null mouse model of sudden unexpected death in epilepsy (SUDEP). Hum Mol Genet 2017;26:2091-103.
112. Gardella E, Marini C, Trivisano M, Fitzgerald MP, Alber M, et al. The phenotype of SCN8A developmental and epileptic encephalopathy. Neurology 2018;91:e1112-24.
113. Anand G, Collett-White F, Orsini A, Thomas S, Jayapal S, et al. Autosomal dominant SCN8A mutation with an unusually mild phenotype. Eur J Paediatr Neurol 2016;20:761-5.
114. Gardella E, Becker F, Møller RS, Schubert J, Lemke JR, et al. Benign infantile seizures and paroxysmal dyskinesia caused by an SCN8A mutation. Ann Neurol 2016;79:428-36.
115. Anderson LL, Thompson CH, Hawkins NA, Nath RD, Petersohn AA, et al. Antiepileptic activity of preferential inhibitors of persistent sodium current. Epilepsia 2014;55:1274-83.
116. Lopez-Santiago LF, Yuan Y, Wagnon JL, Hull JM, Frasier CR, et al. Neuronal hyperexcitability in a mouse model of SCN8A epileptic encephalopathy. Proc Natl Acad Sci U S A 2017;114:2383-8.
117. Patel RR, Barbosa C, Brustovetsky T, Brustovetsky N, Cummins TR. Aberrant epilepsy-associated mutant Nav1.6 sodium channel activity can be targeted with cannabidiol. Brain 2016;139:2164-81.
118. Watanabe Y, Kimura J. Inhibitory effect of amiodarone on Na(+)/Ca(2+) exchange current in guinea-pig cardiac myocytes. Br J Pharmacol 2000;131:80-4.
119. Watanabe Y, Kimura J. Blocking effect of bepridil on Na+/Ca2+ exchange current in guinea pig cardiac ventricular myocytes. Jpn J Pharmacol 2001;85:370-5.
120. Watanabe Y, Iwamoto T, Shigekawa M, Kimura J. Inhibitory effect of aprindine on Na+/Ca2+ exchange current in guinea-pig cardiac ventricular myocytes. Br J Pharmacol 2002;136:361-6.
121. Yamakawa T, Watanabe Y, Watanabe H, Kimura J. Inhibitory effect of cibenzoline on Na+/Ca2+ exchange current in guinea-pig cardiac ventricular myocytes. J Pharmacol Sci 2012;120:59-62.
122. Pena SD, Coimbra RL. Ataxia and myoclonic epilepsy due to a heterozygous new mutation in KCNA2: proposal for a new channelopathy. Clin Genet 2015;87:e1-3.
123. Jouvenceau A, Eunson LH, Spauschus A, Ramesh V, Zuberi SM, et al. Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel. Lancet 2001;358:801-7.
124. Xie G, Harrison J, Clapcote SJ, Huang Y, Zhang JY, et al. A new Kv1.2 channelopathy underlying cerebellar ataxia. J Biol Chem 2010;285:32160-73.
125. Imbrici P, Jaffe SL, Eunson LH, Davies NP, Herd C, et al. Dysfunction of the brain calcium channel CaV2.1 in absence epilepsy and episodic ataxia. Brain 2004;127:2682-92.
126. Damaj L, Lupien-Meilleur A, Lortie A, Riou É, Ospina LH, et al. CACNA1A haploinsufficiency causes cognitive impairment, autism and epileptic encephalopathy with mild cerebellar symptoms. Eur J Hum Genet 2015;23:1505-12.
127. Hino-Fukuyo N, Kikuchi A, Arai-Ichinoi N, Niihori T, Sato R, et al. Genomic analysis identifies candidate pathogenic variants in 9 of 18 patients with unexplained West syndrome. Hum Genet 2015;134:649-58.
128. Reinson K, Õiglane-Shlik E, Talvik I, Vaher U, Õunapuu A, et al. Biallelic CACNA1A mutations cause early onset epileptic encephalopathy with progressive cerebral, cerebellar, and optic nerve atrophy. Am J Med Genet A 2016;170:2173-6.
129. Cramer SW, Popa LS, Carter RE, Chen G, Ebner TJ. Abnormal excitability and episodic low-frequency oscillations in the cerebral cortex of the tottering mouse. J Neurosci 2015;35:5664-79.
130. Zamponi GW. Targeting voltage-gated calcium channels in neurological and psychiatric diseases. Nat Rev Drug Discov 2016;15:19-34.
131. Song I, Kim D, Choi S, Sun M, Kim Y, et al. Role of the 1G T-type calcium channel in spontaneous absence seizures in mutant mice. J Neurosci 2004;24:5249-57.
132. Nava C, Dalle C, Rastetter A, Striano P, de Kovel CG, et al. De novo mutations in HCN1 cause early infantile epileptic encephalopathy. Nat Genet 2014;46:640-5.
133. Savelieva I, Camm A. Novel If current inhibitor ivabradine: safety considerations. In: Camm A, Tendera M, editors. Heart rate slowing by If

current inhibition. Basel: Karger; 2006. p. 79-96.
134. Cacheaux LP, Topf N, Tibbs GR, Schaefer UR, Levi R, et al. Impairment of hyperpolarization-activated, cyclic nucleotide-gated channel function by the intravenous general anesthetic propofol. J Pharmacol Exp Ther 2005;315:517-25.
135. Lyashchenko AK, Redd KJ, Yang J, Tibbs GR. Propofol inhibits HCN1 pacemaker channels by selective association with the closed states of the membrane embedded channel core. J Physiol 2007;583:37-56.
136. Poolos NP, Migliore M, Johnston D. Pharmacological upregulation of h-channels reduces the excitability of pyramidal neuron dendrites. Nat Neurosci 2002;5:767-74.
137. Surges R, Freiman TM, Feuerstein TJ. Gabapentin increases the hyperpolarization-activated cation current Ih in rat CA1 pyramidal cells. Epilepsia 2003;44:150-6.
138. Strauss U, Kole MH, Bräuer AU, Pahnke J, Bajorat R, et al. An impaired neocortical Ih is associated with enhanced excitability and absence epilepsy. Eur J Neurosci 2004;19:3048-58.
139. Ghasemi M, Hadipour-Niktarash A. Pathologic role of neuronal nicotinic acetylcholine receptors in epileptic disorders: implication for pharmacological interventions. Rev Neurosci 2015;26:199-223.
140. Becchetti A, Aracri P, Meneghini S, Brusco S, Amadeo A. The role of nicotinic acetylcholine receptors in autosomal dominant nocturnal frontal lobe epilepsy. Front Physiol 2015;6:22.
141. Howell KB, Eggers S, Dalziel K, Riseley J, Mandelstam S, et al. A population-based cost-effectiveness study of early genetic testing in severe epilepsies of infancy. Epilepsia 2018;59:1177-87.
142. Córdoba M, Rodriguez-Quiroga SA, Vega PA, Salinas V, Perez-Maturo J, et al. Whole exome sequencing in neurogenetic odysseys: an effective, cost- and time-saving diagnostic approach. PLoS One 2018;13:e0191228.
143. Orsini A, Zara F, Striano P. Recent advances in epilepsy genetics. Neurosci Lett 2018;667:4-9.