



Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet



Review article

Pharmacogenomics in epilepsy

Simona Balestrini^{a,b}, Sanjay M. Sisodiya^{a,*}

^a NIHR University College London Hospitals Biomedical Research Centre, Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, London, and Epilepsy Society, Chalfont-St-Peter, Bucks, United Kingdom

^b Neuroscience Department, Polytechnic University of Marche, Ancona, Italy

HIGHLIGHTS

- Genetic variation can influence response to antiepileptic drug (AED) treatment through various effector processes.
- Metabolism of many AEDs is mediated by the cytochrome P450 (CYP) family; some of the CYPs have allelic variants that may affect serum AED concentrations.
- 'Precision medicine' focuses on the identification of an underlying genetic aetiology allowing personalised therapeutic choices.
- Certain human leukocyte antigen, *HLA*, alleles are associated with an increased risk of idiosyncratic adverse drug reactions.
- New results are emerging from large-scale multinational efforts, likely imminently to add knowledge of value from a pharmacogenetic perspective.

ARTICLE INFO

Article history:

Received 16 November 2016
Received in revised form 5 January 2017
Accepted 6 January 2017
Available online xxx

Keywords:

Pharmacokinetics
Pharmacodynamics
Precision medicine
Epilepsy
Drug resistance
Drug response
Adverse drug reactions
Pharmacogenomics

ABSTRACT

There is high variability in the response to antiepileptic treatment across people with epilepsy. Genetic factors significantly contribute to such variability. Recent advances in the genetics and neurobiology of the epilepsies are establishing the basis for a new era in the treatment of epilepsy, focused on each individual and their specific epilepsy. Variation in response to antiepileptic drug treatment may arise from genetic variation in a range of gene categories, including genes affecting drug pharmacokinetics, and drug pharmacodynamics, but also genes held to actually cause the epilepsy itself.

From a purely pharmacogenetic perspective, there are few robust genetic findings with established evidence in epilepsy. Many findings are still controversial with anecdotal or less secure evidence and need further validation, e.g. variation in genes for transporter systems and antiepileptic drug targets. The increasing use of genetic sequencing and the results of large-scale collaborative projects may soon expand the established evidence.

Precision medicine treatments represent a growing area of interest, focussing on reversing or circumventing the pathophysiological effects of specific gene mutations. This could lead to a dramatic improvement of the effectiveness and safety of epilepsy treatments, by targeting the biological mechanisms responsible for epilepsy in each specific individual.

Whilst much has been written about epilepsy pharmacogenetics, there does now seem to be building momentum that promises to deliver results of use in clinic.

© 2017 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. Introduction.....	00
1.1. Influence of genetic factors on response to AEDs.....	00
1.2. Pharmacokinetics and pharmacodynamics.....	00
2. Established evidence.....	00
3. Less robust evidence.....	00
4. Unclear evidence.....	00
4.1. Epilepsy genes.....	00
5. Established evidence.....	00

* Corresponding author at: Department of Clinical and Experimental Epilepsy, UCL Institute of Neurology, Queen Square, London, WC1N 3BG, UK.
E-mail address: s.sisodiya@ucl.ac.uk (S.M. Sisodiya).

<http://dx.doi.org/10.1016/j.neulet.2017.01.014>

0304-3940/© 2017 The Authors. Published by Elsevier Ireland Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Please cite this article in press as: S. Balestrini, S.M. Sisodiya, Pharmacogenomics in epilepsy, Neurosci. Lett. (2017), <http://dx.doi.org/10.1016/j.neulet.2017.01.014>

6.	Less robust evidence	00
6.1.	Influence of genetic factors on adverse drug reactions	00
7.	Established evidence	00
8.	Unclear evidence	00
8.1.	Future of pharmacogenomics: new paradigms for testing and translation?	00
	Funding	00
	Acknowledgement	00
	References	00

1. Introduction

The response, in terms both of seizure control and adverse reactions (ADRs), to antiepileptic drugs (AEDs) varies greatly across individuals [1]. Moreover, AED treatment in epilepsy is complicated because there are many different syndrome and seizure types within epilepsy, the biology of almost all of which is largely unknown. Response rates do seem to vary in relation to epilepsy syndrome, underlying cause, and other factors [2,3]. The broad phenotypic spectrum and heterogeneous aetiology make the choice of treatment both challenging and empirical: evidence-based information guiding clinicians on the most effective drug and dose for individual patients is lacking. Furthermore, AEDs can have many associated ADRs, some of which are severe and life-threatening [4]. A cross-sectional survey of 809 patients showed that 36.5% experienced one or more ADRs; these events were not related to the number of AEDs, but rather to individual susceptibility, the specific AED used and physicians' skills [5].

There is established evidence that genetic factors certainly contribute to this variability [6]. However, few robust findings have clearly emerged in epilepsy. Progress since the most recent comprehensive reviews [6,7] has been limited. The increasing application of massively-parallel genetic sequencing and results of collaborative projects (such as EpiPGX, <http://www.epipgx.eu> and CPNDS, <http://cpnds.ubc.ca/>) may soon expand knowledge in this area.

Recent advances in the genetics and neurobiology of the epilepsies are establishing the basis for a new era in the treatment of epilepsy, focused on each individual and their particular epilepsy. Testing for gene variations that might predict drug response and ADRs will hopefully soon improve the efficacy and safety of epilepsy therapies, targeting the best drug from those available for each individual patient. Increasing knowledge of the biology of the epilepsies may also lead to the re-purposing for epilepsy of drugs not originally intended for use in epilepsy, and may also direct discovery of rational new therapies. Moreover, as more is becoming understood, it is also clear that in some cases, there is important overlap between disease causation and the profile of response to AEDs.

There remains much to be learnt about epilepsy pharmacogenomics: any classification is necessarily arbitrary. Here, we distinguish the influence of genetic factors on response to AEDs from those affecting adverse drug reaction. We further classify the former according to the mediating mechanisms: pharmacokinetics and pharmacodynamics, or genes mutations which are recognised as capable of causing epilepsy ('epilepsy genes'). This should be considered as an evolving classification. Despite ongoing progress in the field, only some findings are accepted within the community so far, whilst many results have not been replicated, and might be specific to certain populations. Below, we present the state of the art, by reporting first the findings with the best established evidence, followed by those with less certain status.

1.1. Influence of genetic factors on response to AEDs

Genetic variation can influence response to AEDs through various mediating effector systems, including pharmacokinetics and

pharmacodynamics (e.g. polymorphism in gene encoding drug metabolizing enzymes or putative brain AED targets, such as receptors or ion channels), and mutations in 'epilepsy genes'; and by modifying the expression of enzymes and other molecules involved in the pathogenesis of pharmacoresistance or adverse drug reactions [8,9]. A key problem is that the mechanistic basis of pharmacoresistance, especially resistance to multiple AEDs, is not understood in the vast majority of cases; nor is the overlap between drug resistance and disease causation well understood [10].

1.2. Pharmacokinetics and pharmacodynamics

In humans, metabolism of those AEDs that undergo such processes is mostly mediated by the cytochrome P450 (CYP) family. Some of the CYPs have genetic (allelic) variants, encoding isoforms of differing activity, which in turn may affect serum AED concentrations, or alter flux through paths for drug metabolism, with subsequent potential risk of drug toxicity.

2. Established evidence

There is established evidence of an effect of polymorphic *CYP2C9* and *CYP2C19* genes: variant alleles can lead to significant differences in AED serum concentrations [11]. *CYP2C9* accounts for about 90% of the metabolism of phenytoin. *CYP2C9* polymorphisms are an important determinant of the rate of phenytoin metabolism. Individuals carrying *CYP2C9* alleles encoding variant enzymes (allozymes) with reduced activity metabolize phenytoin at a considerably slower rate compared with individuals homozygous for the wild-type (*CYP2C9*1*; rs1057910(A)) allele, and therefore have a greater risk of developing concentration-dependent neurotoxicity: *CYP2C9*2* (rs1799853) and *CYP2C9*3* (rs1057910(C)) are the best documented [12,13]. The maximum dose of phenytoin reported in a series of people with epilepsy was about 50 mg less per *CYP2C9*3* allele [14].

A genome-wide association study of cases with phenytoin-related severe cutaneous adverse reactions and 412 population controls from Taiwan discovered a cluster of 16 single nucleotide polymorphisms in *CYP2C* genes at 10q23.33 that reached genome-wide significance. Direct sequencing of *CYP2C9* identified missense variant rs1057910 (*CYP2C9*3*) as showing significant association with phenytoin-related severe cutaneous adverse reactions [15]. The mechanism underlying this association has yet to be established. Despite the available evidence, pre-treatment pharmacogenetic testing for *CYP2C9* variants is not routine practice, with monitoring for clinical signs of toxicity and serum drug level being the standard approach.

3. Less robust evidence

Few, and mostly preliminary, data are available on genetic factors influencing the metabolism of other AEDs.

Studies investigated the association between *CYP2C19* genotypes and the pharmacokinetics of clobazam and N-desmethylclobazam (N-clobazam), a pharmacologically active

metabolite that reaches higher serum concentrations than clobazam [16]. *CYP2C19* polymorphisms were associated with the serum concentration of N-clobazam and with clinical efficacy, thus indicating a gene-dose effect [17–21]. These were conducted mostly in Asian populations, and have not been replicated more widely.

Genetic influences on phenobarbital metabolism seem to relate mostly to *CYP2C19* polymorphism, with ethnic differences in the tolerability profile of phenobarbital [22]. However, there is absence of evidence that genotyping improves the outcome of phenobarbital therapy compared with clinical observation and serum drug concentration monitoring.

Valproate (VPA) is subject to complex oxidative and non-oxidative metabolic pathways. The majority of the drug is eliminated as glucuronide conjugates. Mitochondrial beta-oxidation, producing unsaturated metabolites, is the second major metabolic pathway. About 15–20% of the VPA dose is metabolized by CYP enzymes, resulting in the formation of 4-ene-VPA and hydroxy-metabolites [23]. The main enzyme for hydroxylation and desaturation to 4-ene-VPA is *CYP2C9*, with minor contributions from *CYP2A6* and *CYP2B6* [24].

Lamotrigine is eliminated almost entirely by glucuronidation. A previous pharmacokinetic study [25] found that in seven individuals with Gilbert's syndrome (unconjugated hyperbilirubinaemia due to genetically-determined deficiency in uridine diphosphate glucuronosyltransferase, UGT), lamotrigine clearance was lower than in healthy controls. The pharmacogenetic impact of this in epilepsy is unknown.

Zonisamide is eliminated via renal excretion of the 2-sulfamoyl-acetyl-phenol (SMAP)-glucuronide (50%), native unchanged form (35%) and N-acetyl zonisamide (15%) [26]. In vitro data showed that the formation of SMAP is catalyzed mainly by *CYP3A4* and to a minor extent by *CYP3A5* and *CYP2C19* [27]. Okada et al. [28] found that *CYP2C19* genotypes may influence the pharmacokinetics of zonisamide, with a role in the development of some adverse reactions, in Japanese patients with epilepsy. Again, these findings need replication.

Carbamazepine is extensively metabolized in the liver, with less than 5% of an oral dose excreted unchanged in urine [29]. Carbamazepine is predominantly metabolized to carbamazepine-10,11-epoxide by *CYP3A* enzymes. The main enzyme involved in its metabolism, *CYP3A4*, has a high number of known polymorphisms although most have a very low frequency and do not reflect significant inter-individual variability in the phenotypic effect in vivo [30]. Carbamazepine-10,11-epoxide and carbamazepine-10,11-*trans*-diol are the primary ($\leq 60\%$) metabolites in urine [31]. Many CYP enzymes are involved in the formation of carbamazepine metabolites [32] but no significant contribution of CYP genotypes to the pharmacokinetics of carbamazepine has been demonstrated so far. Single nucleotide polymorphisms of the microsomal epoxide hydrolase (*EPHX1*) gene have been shown to affect carbamazepine pharmacokinetics in Chinese people with epilepsy [33], and in Kosovan people with epilepsy of Albanian ethnicity [34].

A further series of reports are all in need of replication. Retigabine is metabolized by extensive N-glucuronidation and N-acetylation. However, its clearance seems not to be affected in Gilbert's syndrome nor by common N-acetyl-transferase type 2 (*NAT-2*) polymorphisms [35]. A study in Han Chinese people with epilepsy found an association between the effects of *SCN1A*, *ABCC2* and *UGT2B7* genetic polymorphisms and oxcarbazepine maintenance doses [36]. Genetic contribution of *CYP1A1* alleles on treatment outcome in people with epilepsy was studied in an Indian population. In particular, the variant rs2606345 (resulting in reduced *CYP1A1* expression) was associated with poor response to first-line AEDs in Indian women with epilepsy [37,38].

4. Unclear evidence

Drug transporters are involved in the protection of cells and organs through active extrusion of xenotoxins, including many drugs. Several ATP-dependent transport proteins have been associated with drug resistance. One of the best studied transporters is P-glycoprotein (P-gp), encoded by the ATP-binding cassette sub-family B member 1 gene, *ABCB1* [39]. In the brain, P-gp is expressed in astrocytes, endothelial cells and neurons, and there is evidence that its overexpression in epileptogenic tissue can contribute to AED resistance [40]. Several studies have demonstrated a link between *ABCB1* gene variants and the response to treatment in epilepsy, but most studies have in fact been inconclusive [41–44]. A recent meta-analysis including 8,604 subjects from 30 studies identified a significant correlation between the *ABCB1* C3435T polymorphism and drug-resistant epilepsy, a result that needs to be verified in a case-control study with a larger sample size, as acknowledged by the authors [45]. Evidence for an association of *ABCB1* polymorphisms with AED resistance is still unclear and does not justify routine testing to predict response to AED therapy.

There have been associations reported for variation in other transporter-encoding genes and treatment-resistant epilepsy [36,46–48], but the strength of evidence is less still than that for *ABCB1*.

Research into polymorphisms affecting genes encoding AED targets, such as voltage-gated ion channels [49,50], the GABA-A receptor [51], or synaptic vesicle proteins [52], has not found any significant association with drug response [53]. More data are likely to emerge in this area as large consortia sequencing large numbers of people with epilepsy report their findings.

4.1. Epilepsy genes

'Precision medicine' is an approach for disease treatment and prevention based on individual variability in genes, environment, and lifestyle for each person [54]. This approach, incorporating the identification of an underlying genetic aetiology to allow personalised therapeutic choice, or to drive re-purposing of drugs, builds upon thoughtful clinical practice that has been applied for years. The 'precision medicine' paradigm has become more realistic with advances in discovery of more of the putative causes of epilepsy in individual patients, and with the wider availability of the necessary genetic technologies [9,55,56]. Formal quantitative evaluation of environmental variables is still largely unaddressed, whilst lifestyle issues have always featured in any holistic approach to the delivery of care.

In epilepsy, if a specific gene mutation causes a functional alteration of physiological systems involved in the control of brain excitability, a rational treatment strategy might ideally aim to reverse or circumvent the dysfunction. This approach may not always prove successful, however, for a number of reasons, including the fact that no causal variant acts in isolation, but does so in the context of the rest of the genome and its variation, and because compensatory and adaptive changes may become fixed and difficult, or impossible, to reverse with treatment of the perceived original fault. The current targeted treatment approach in precision medicine requires the identification of the underlying causative genetic alteration, determination of the functional alteration of the physiological system caused by the genetic mutation, and evaluation of the effect of treatment putatively intended and able to reverse or inhibit the functional alteration.

The current evidence is ordered by the robustness of the available evidence.

5. Established evidence

An established example of the application of the precision medicine concept is in the management of GLUT-1 deficiency, a genetic metabolic encephalopathy due to mutations in the *SLC2A1* gene, which encodes the glucose type I transporter (GLUT-1), resulting in impaired transport of glucose across the blood-brain barrier. GLUT-1 deficiency shows wide phenotypic pleiotropy, including intellectual disability, movement disorder, and drug-resistant epilepsy, as AEDs usually fail to control seizures. The gold standard treatment is the ketogenic diet, which provides ketones as an alternative fuel for cerebral metabolism, thereby treating the symptoms of neuroglycopenia [57]. Early diagnosis and initiation of ketogenic diet are crucial to provide brain nourishment and control seizures [58], although the benefit on neurodevelopment seems controversial [59]. The challenge is to think of GLUT-1 deficiency as a possible diagnosis, an issue shared by many genetic diagnoses in epilepsy because of the pleiotropic manifestations of many mutated genes: the use of gene panels or more extensive sequencing (exome or genome) can help overcome this difficulty.

Pyridoxine (vitamin B6)-dependent epilepsy is caused by biallelic mutations in the *ALDH7A1* gene, which encodes antiquitin. Deficiency of antiquitin causes seizures because accumulating Δ^1 -piperidine-6-carboxylate (P6C) condenses with pyridoxal 5'-phosphate (PLP) and inactivates this enzyme cofactor, which is essential for normal metabolism of neurotransmitters. *ALDH7A1* analysis could also be used for prenatal diagnosis of pyridoxine-dependent epilepsy and seizures are often fully controlled by treatment with pyridoxine [60]. B6-responsive seizures may also be due to mutations in pyridox(am)ine 5'-phosphate oxidase (*PNPO*) gene, and in some cases may be better treated with pyridoxal 5'-phosphate [61].

6. Less robust evidence

Other recent reports hint at the potential relevance of precision medicine in epilepsy, by investigating the effect of treatment of the molecular defects resulting from specific mutation in certain genes. There are few examples so far and most are anecdotal.

Dravet Syndrome is a severe epilepsy syndrome of early childhood, associated with drug resistance, developmental slowing or regression and intellectual disability, and risk of premature mortality, including sudden unexpected death in epilepsy (SUDEP). It is perhaps the best understood genetic epilepsy and has advanced understanding not only of concepts in disease biology, but also of treatment biology and genetics. The most frequent cause of Dravet Syndrome is mutation in the voltage-gated sodium channel $\alpha 1$ subunit gene (*SCN1A*). Mutations in *SCN1A* are also associated with milder phenotypes, such as genetic epilepsy with febrile seizures plus (GEFS+) [62]. Though of all the epilepsies (especially the non-metabolic ones), we understand Dravet Syndrome the best, its pathophysiology has not been fully explained yet and this makes the development of targeted treatment more complicated. The "interneurone hypothesis" is currently the best-supported pathophysiological explanation of Dravet Syndrome. According to this hypothesis, *SCN1A* mutation results in reduced function of GABAergic inhibitory interneurons, leading to an overall excessive neuronal excitation [63–65]. However, other studies using Dravet Syndrome patient-derived induced pluripotent stem cells (iPSC) found increased excitability of both GABAergic and glutamatergic isolated neurons [66]. A recent study identified a depolarizing GABA phenomenon, and explored the mechanism of action of benzodiazepines and stiripentol, commonly beneficial in Dravet Syndrome, by using a physiology-based computational model [67]. It is still unclear if major manifestations of the disease

are caused by disturbances in embryonic development or by persistent *SCN1A* deficiency in later life. It is also not known if increasing *SCN1A* expression after birth would alter the disease phenotype. A recent study demonstrated a new regulatory mechanism of *SCN1A* expression, by targeting a long non-coding RNA, both in vitro and in vivo, in the brain of Dravet knock-in mouse model and a non-human primate (African green monkey model); upregulation of haploinsufficient *SCN1A* expression led to significant improvements in seizure phenotype and excitability of hippocampal interneurons [68]. As a paradigmatic epileptic encephalopathy, Dravet Syndrome still has much to teach us.

Currently, treatment of Dravet Syndrome typically involves polytherapy with valproate, clobazam and often stiripentol. Evidence for many drugs favoured in Dravet Syndrome is in fact sparse [69]. Stiripentol is the only compound to have efficacy in Dravet Syndrome formally demonstrated in a randomised controlled trial (when combined with valproate and clobazam; [70]); however, the use of stiripentol, valproate and clobazam does not always yield complete seizure freedom and may cause adverse side effects [71,72]. New and effective treatment strategies with possibly novel mechanisms are therefore needed.

Many model systems have been employed to explore the cellular mechanisms of seizure genesis caused by different *SCN1A* mutations [73]. Heterologous expression systems, in which cloned sodium channel α -subunits are expressed in an intrinsically non-excitable cell, were the first models used to investigate the cellular consequences of *SCN1A* mutations associated with epilepsy. Studies in heterologous systems were the first to demonstrate that *SCN1A* mutations can cause both gain and loss of function at the channel level [74]. There is now growing evidence that epileptogenic *SCN1A* mutations cause mainly loss of function, whereas gain of function is found for mutations that cause familial hemiplegic migraine [75]. Heterologous expression systems have been used for testing compounds that modulate voltage-gated sodium channels. For example, ranolazine, a U.S. Food and Drug Administration (FDA)-approved drug for chronic angina treatment, was first identified as a selective blocker of persistent currents in mutant $Na_v1.1$ channels expressed in one of these models [76]. In follow-up studies in cultured rat hippocampal neurons, ranolazine was found to reduce neuronal excitability and suppress epileptiform activity evoked by NMDA receptor activation [77]. A more recent study showed that ranolazine does not inhibit the persistent Na^+ current more strongly than phenytoin in central neurons, but is a better use-dependent blocker of transient Na^+ current than phenytoin [78]. Furthermore, identifying compounds that can differentially modulate different subtypes/isoforms of sodium channels may contribute to identifying new treatment strategies for *SCN1A*-related epilepsy [79]. Mouse models have shown how the same *SCN1A* mutation can have differential effects on different types of neurons, and how the same type of mutation, such as *SCN1A* truncations, may have different effects on neuronal excitability depending on developmental stage [65,80].

Baraban et al. [81] characterised zebrafish $Na_v1.1$ (*scn1Lab*) mutants originally identified in a chemical mutagenesis screen using the optokinetic response as an assay [82]. The zebrafish *scn1Lab* gene shares a 77% identity with human *SCN1A* and is expressed in the central nervous system. Baraban et al. [81] demonstrated that mutants exhibit hyperactivity, including convulsive behaviour, spontaneous electrographic seizures, shortened lifespan and a pharmacological profile similar to the human condition. They then used the validated model in a novel high-throughput screening program to identify compounds that ameliorated the epilepsy phenotype. The strategy identified clemizole, a US Food and Drug Administration (FDA)-approved compound but not a licensed AED, as an effective inhibitor of spontaneous convulsive behaviour and electrographic seizures in these mutants. There have

been no further reports on clemizole use in Dravet Syndrome or models. Recent data suggest that fenfluramine may be effective in Dravet syndrome [83,84]. This drug was initially developed as an appetite suppressant, but withdrawn from the market due to serious adverse effects, including valvular heart disease and pulmonary hypertension [85,86]. Fenfluramine has serotonergic effects [87], but the exact anti-seizure mechanism has not been elucidated yet. Fenfluramine significantly reduced epileptiform discharges in *scn1Lab* morphants in recent studies [88,89]. Currently there are four ongoing clinical trials to evaluate the effectiveness and tolerability of this drug in Dravet Syndrome. A functional link between the serotonergic and GABAergic pathway has recently been elucidated since 5-HT_{2A} agonism elevates the activity of GABAergic interneurons [90]. A recent study in zebrafish suggested a dual mechanism in Dravet Syndrome pathophysiology, postulating that GABA interneurons are defective, not only due to presence of mutations but also by a relative deficiency in locally released serotonin [91]. If confirmed, this supports serotonergic receptor modulation as a promising therapeutic target in Dravet Syndrome.

Some patients with Dravet Syndrome have seizure aggravation with exposure to sodium channel blockers, e.g. carbamazepine, lamotrigine and phenytoin [92]. As Na_v1.1 shows higher expression in inhibitory bipolar as compared to excitatory pyramidal neurons [93], it can be hypothesized that the effect of sodium channel blockers on already impeded inhibitory interneurons outweighs the effect on excitatory neurons leading to a further decrease in inhibition and seizure exacerbation. However, it has been shown how lamotrigine can improve seizure control in some patients with Dravet Syndrome [94]. All these findings show how treatment response maybe specific to the nature and the location of the *SCN1A* mutation [75,95], and offers up a somewhat daunting perspective of precision medicine in the epilepsies.

The NMDA receptor is a ligand-gated ion channel activated by glutamate. *GRIN2A* encodes a subunit of the NMDA receptor. Mutations and deletions in the *GRIN2A* gene predispose to several childhood-onset epilepsy syndromes within the epilepsy-aphasia spectrum, including Landau-Kleffner syndrome (LKS), epileptic encephalopathy with continuous spike-and-wave during sleep (ECSWS), childhood epilepsy with centrotemporal spikes (CECTS), atypical childhood epilepsy with centrotemporal spikes (ACECTS), autosomal dominant rolandic epilepsy with speech dyspraxia (ADRES), and infantile-onset epileptic encephalopathy [96–100]. Under normal conditions of synaptic transmission, very few ions pass through the channel because magnesium (Mg²⁺) blocks the pore. Upon receptor activation, Mg²⁺ is displaced, which allows calcium (Ca²⁺) and other cations to move into the cell. A dysfunctional NMDA receptor can allow excess calcium influx into the cell. In vitro experiments testing activity of a *GRIN2A* mutant (L812M) receptor showed increased activity in response to agonists and decreased response to negative modulators [101]. In vitro analysis showed that memantine, a *N*-methyl-*D*-aspartate (NMDA) receptor antagonist, inhibited the increased activity of the NMDA receptor caused by the L812M mutation. A child with an early onset epileptic encephalopathy due to this *GRIN2A* missense mutation (L812M) [102] was treated with memantine added on to his antiepileptic medication regimen, and had a significant decrease in seizure frequency and improvement in interictal EEG recordings. In contrast, another child's epileptic encephalopathy was found to be caused by a different *GRIN2A* missense mutation (N615K) causing a different channel dysfunction, with no effect on receptor activity, but acting through the relief of Mg²⁺ blockade [96]. Treatment with memantine was therefore not tried in this case, as it was not indicated.

A child with a different epilepsy syndrome, migrating partial seizures of infancy (an early onset epileptic encephalopathy syndrome which is typically drug-resistant), due to a gain of function mutation in the gene *KCNT1*, was treated with the antiarrhythmic

drug quinidine. This drug is a partial antagonist of KCNT1, and the treatment was associated with a marked reduction in seizure frequency and improved psychomotor development [103]. Quinidine was previously used to reverse the hyperactivity of the mutant *KCNT1* in *Xenopus* oocytes [104]. A second case with *KCNT1*-related epilepsy, showing a novel phenotype with developmental regression and severe nocturnal focal and secondarily generalised seizures starting in early childhood, did not respond to treatment with quinidine [105]. Currently the therapeutic effects of quinidine in *KCNT1*-related epilepsy remain largely unknown and more work is required, although it seems a promising treatment option due to gain-of-function mutations in *KCNT1*.

KCNQ2-related epilepsy is another example where a molecular diagnosis may influence the therapeutic choice. Retigabine (ezogabine), is a drug primarily acting as a positive allosteric modulator of KCNQ2-5 (K_v7.2–7.5) ion channels: it is the first neuronal potassium (K⁺) channel opener licensed for the treatment of epilepsy [106]. In vitro studies identified the probable binding site of retigabine in KCNQ2 and KCNQ3 channels, explaining its voltage-dependent activating effect through a hyperpolarizing shift of the activation curve [107,108]. *KCNQ2* and *KCNQ3* mutations have been associated with a phenotypic spectrum ranging from a benign form of neonatal epilepsy (BFNS) [109] to a severe form of early-onset epileptic encephalopathy [110,111]. Orhan et al. [112] defined the disease mechanism of seven de novo missense *KCNQ2* mutations associated with severe epileptic encephalopathy and found a clear loss of function for all the mutations studied in vitro. Most mutations showed a dominant-negative effect on wild-type KCNQ2 or KCNQ3 subunits. The use of retigabine partially reversed the loss of function, in vitro, for the majority of analyzed mutations. Preliminary data from humans with *KCNQ2*-related disease suggest retigabine may be a useful treatment option [113], but more data are required. Sodium channel blockers also seem effective in *KCNQ2*-related epilepsy [111,114], possibly because voltage-gated sodium channels and KCNQ potassium channels co-localize and are bound at critical locations of the neuronal membrane [115]; modulation of one channel may significantly affect the function of the channel complex and this may explain the efficacy of sodium-channel blockers that have a modulating effect on both channels [111]. Sodium channel blockers including carbamazepine and phenytoin should also be considered as first-line treatment in patients with *KCNQ2*-related epilepsy [116].

SCN2A encodes the alpha2 subunit of the neuronal sodium channel and has also been associated with a wide phenotypic spectrum of epilepsy syndromes ranging from benign familial neonatal-infantile seizures to epilepsy of infancy with migrating focal seizures or other severe epileptic encephalopathies [117–119]. Sodium channel blockers have shown significant effectiveness in *SCN2A*-epileptic encephalopathies. The mechanism of the effect has not been elucidated yet, but, as might be expected, the effect seems mostly present in patients with gain-of-function mutations [118,119]. An anecdotal case with a de novo *SCN2A* splice site mutation associated with epileptic encephalopathy, early onset global developmental delay, intermittent ataxia, autism, hypotonia, and cerebellar/cerebellar atrophy was recently reported. In the cerebrospinal fluid, both homovanillic acid and 5-hydroxyindoleacetic acid were significantly decreased; extensive biochemical and genetic investigations ruled out primary neurotransmitter deficiencies and other known inborn errors of metabolism. Treatment with oral 5-hydroxytryptophan, l-Dopa/Carbidopa, and a dopa agonist resulted in mild improvement of seizure control, most likely via dopamine and serotonin receptor activated signal transduction and modulation of glutamatergic, GABA-ergic and glycinergic neurotransmission [120]. This single case hints at the complexity that is likely to be observed when additional or compensatory changes are present in 'monogenic' epilepsies.

SCN8A encodes the voltage-dependent sodium channel $Na_v1.6$, located in both inhibitory and excitatory neurons [121]. Mutations in this gene have been found in 0.6–2.4% of cases with early infantile epileptic encephalopathy [122,123] and have been associated with increased risk of SUDEP [121,123–125]. In most cases, *SCN8A* mutations occurred de novo and showed a gain-of-function effect [121,126]. There is clinical evidence of a possible effective precision medicine approach in using sodium channel blockers to treat patients with *SCN8A*-related epilepsy [121,123,127], in particular if the mutations are known to cause gain of function [128].

Tuberous sclerosis complex (TSC) is an autosomal dominant, multi-organ disease with widely variable clinical expression. Approximately 85% of patients with TSC are found to have a mutation in one of two genes, *TSC1*, encoding hamartin, or *TSC2*, encoding tuberin [129]. Protein products of these genes have been shown to form a heterodimer (TSC1–TSC2 complex) that inhibits the mechanistic target of rapamycin (mTOR) signaling cascade [130]. The mTOR signaling cascade regulates processes involved in cell growth and homeostasis in response to many metabolic cues. Dysregulated, inadequate suppression of the mTOR pathway results in dysplastic lesions in multiple organ systems, including cortical tubers, radial glial bands, subependymal nodules, and subependymal giant cell tumor formation in the fetal and developing brain [131]. Epilepsy is the most common neurologic symptom in patients with TSC [132]. Rapamycin (otherwise known as sirolimus) is an inhibitor of mTOR. Rapamycin prevents activation of T cells and B cells by inhibiting their response to interleukin-2 (IL-2), and is an FDA-approved drug for immunosuppression after organ transplantation. A clinical trial of rapamycin for renal angiomyolipomata associated with tuberous sclerosis or lymphangiomyomatosis revealed an almost 50% decrease in angiomyolipoma volumes by the end of the 12-month rapamycin administration period [133]. A phase 2 multicenter trial was conducted to evaluate the efficacy and tolerability of sirolimus for the treatment of kidney angiomyolipomata [134]. Treatment with sirolimus for 52 weeks induced regression of kidney angiomyolipomata, subependymal giant cell astrocytomas, and liver angiomyolipomata. Another clinical trial was designed to study the impact of everolimus (a derivative of sirolimus) on subependymal giant cell astrocytoma growth and showed sustained effect on tumor reduction over ≥ 5 years of treatment, with no safety concerns [135,136]. Treatment with rapamycin was shown to prevent the development of epilepsy and premature death in mouse models of TSC [137,138]. A few reports in humans have showed significant improvement in seizure control in children and adults with TSC-associated epilepsy, with a tolerable safety profile [139–141]. More studies are needed, and are important as evidence grows for a more widespread dysregulation of the mTOR pathway beyond that seen in TSC alone. One example comes from epilepsies due to mutation in a gene in this pathway.

DEPDC5 (Dishevelled, Egl-10 and Pleckstrin Domain Containing Protein 5) loss-of-function mutations have recently been reported in a variety of genetic focal epilepsy syndromes, including familial focal epilepsy with variable foci, autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy [142–144], rolandic epilepsy and other non-lesional focal childhood epilepsies [145] and focal epilepsy associated with focal cortical dysplasia, both familial and sporadic [146,147]. *DEPDC5* variants have also been found in cases with malformation of cortical development [146,147] and in one sporadic case with focal epilepsy among a cohort of French-Canadian individuals [148]. *DEPDC5* encodes a protein that is expressed ubiquitously in developing and adult brain [142]; it has GTPase-activating protein (GAP) activity and is part of the GATOR1 complex, a negative regulator of the mechanistic target of rapamycin complex 1 (mTORC1), in the mTOR pathway [149]. The mTORC1 pathway is dysregulated in several neurological disorders associated with cortical malformations

and drug-resistant epilepsy, such as tuberous sclerosis [150] and hemimegalencephaly [151]. Because *DEPDC5* acts as a repressor of mTOR activity, *DEPDC5* mutations are predicted to result in upregulation of the mTOR signaling pathway. Prenatal treatment with rapamycin in global *Depdc5* knockout rats rescued growth delay and embryonic lethality, and prevented enhanced cell size and dysmorphism of neurons [152]. Disruption of the mTOR signaling pathway is a putative pathophysiologic mechanism of epileptogenesis in different models of lesional epilepsy in rodents and humans [153] and has emerged as a possible therapeutic target for epilepsy [154]. Deep whole-exome sequencing identified mutations of the *MTOR* gene in 12 of 77 subjects with focal cortical dysplasia type II (FCDII), a sporadic developmental malformation of the cerebral cortex characterised by dysmorphic neurons, dyslamination and medically-refractory epilepsy [155]. The identified mutations induced the hyperactivation of mTOR kinase. Focal cortical expression of mutant mTOR by in utero electroporation in mice was sufficient to disrupt neuronal migration and cause spontaneous seizures and cytomegalic neurons. Inhibition of mTOR with rapamycin suppressed cytomegalic neurons and epileptic seizures, so identifying mTOR as a treatment target for intractable epilepsy in focal cortical dysplasia [155]. Germline heterozygous mutations in the genes encoding the two other components of GATOR1, *NPRL2* (nitrogen permease regulator-like 2), and *NPRL3* (nitrogen permease regulator-like 3), have been reported. An *NPRL3* pathogenic mutation was discovered by whole exome sequencing in a family including four subjects with focal epilepsy, two of whom had focal cortical dysplasia type IIa, and later identified in two additional unrelated patients with focal cortical dysplasia type IIa [156]. A second study using whole exome sequencing in a large family with autosomal dominant nocturnal epilepsy without apparent structural brain abnormalities uncovered an inactivating variant in *NPRL2* [157]. Two other studies identified several *NPRL2* and *NPRL3* mutations in both sporadic and familial focal epilepsies using targeted gene panel sequencing [158,159]. GATOR1 complex gene mutations leading to mTORC1 pathway upregulation are an important cause of focal epilepsy with cortical malformations. Treatment with mTOR inhibitors in patients with gene mutations affecting the GATOR1 complex subunit has not yet been investigated to our knowledge. However pathophysiological similarities between different mTORopathies warrant further studies [146].

PRICKLE proteins, such as PRICKLE1, are core constituents of the planar cell polarity signaling pathway that establishes cell polarity during embryonic development [160]. Mutations in the *PRICKLE* genes can cause seizures in humans, zebrafish, mice, and flies, suggesting a seizure-suppression pathway that may be evolutionarily conserved [161,162]. This pathway has never been targeted for novel anti-seizure treatments. Paemka et al. [163] defined the mammalian PRICKLE-interactome, identifying PRICKLE-interacting proteins that localize to synapses and a novel interacting partner, USP9X, a substrate-specific de-ubiquitinase. Their findings demonstrated that inhibition of USP9X can arrest PRICKLE-mediated seizures. As *PRICKLE* mutant humans, mice, zebrafish, and *Drosophila* all exhibit seizures [162,164], USP9X-modulating molecules may be worth pursuing as a new class of anti-seizure therapy. This represents an example of the translational power of studying diseases in species across the evolutionary spectrum.

Based on all these reports, the ascertainment of a molecular diagnosis early in life and generation and characterization of cell culture and valid animal models for the interpretation of the functional consequences of a mutation, may become fundamental for overall diagnosis, prognosis and therapeutic management. Currently, genetically-targeted therapies are available for only a minority of genetic epilepsies. Such therapies include drugs that exert their effect on ion channels, inhibit the mTOR pathway or

provide alternative energy supply to the brain by avoiding defective transport mechanisms. So far, drugs or treatment that have been investigated were those already available on the market but not necessarily approved for the treatment of epilepsy. Novel drug generation has yet to come.

6.1. Influence of genetic factors on adverse drug reactions

Genetic polymorphisms have been associated with the risk of side effects. In particular, there is extensive evidence of the association between certain human leukocyte antigen (*HLA*) alleles and increased risk of idiosyncratic adverse drug reactions.

7. Established evidence

A strong association was found in people with epilepsy and Han Chinese origin between a genetic marker, *HLA-B*15:02*, and Stevens-Johnson syndrome induced by treatment with carbamazepine, probably due the role of this allele in mediating the activation of cytotoxic T-lymphocytes [165,166]. The frequency of the *HLA-B*15:02* allele is very low in Caucasian people, but high in Han Chinese and other South Asian ethnic groups, including people from Thailand, Malaysia, Vietnam and other South Asian countries: the risk of *HLA-B*15:02*-associated Stevens-Johnson syndrome and toxic epidermal necrolysis is dependent on the specific population. A study conducted in Taiwan showed that screening patients for the *HLA-B*15:02* allele before the initiation of carbamazepine treatment and withholding carbamazepine from *HLA-B*15:02*-carrying patients can reduce the incidence of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis among patients of Han Chinese origin [167]. Regulatory agencies and therapeutic guidelines recommend that patients from Han Chinese and other South Asian ethnic groups be genotyped for *HLA-B*15:02* before commencing treatment with carbamazepine, and that carbamazepine be avoided if at all possible in carriers of this allele [168,169]. The *HLA-B*15:02* allele has also been associated with increased risk of Stevens-Johnson syndrome/toxic epidermal necrolysis after treatment with other aromatic AEDs, including phenytoin [170], oxcarbazepine [171], and lamotrigine [170]. This is the best example of a useful pharmacogenetic variant in epilepsy.

*HLA-A*31:01* has been associated with increased risk of carbamazepine-induced hypersensitivity reactions, ranging from maculopapular exanthema to severe blistering reactions, among subjects of European ancestry and in the Japanese population [172,173]. Recent economic modelling suggested that routine testing for *HLA-A*31:01* in order to reduce the incidence of cutaneous adverse drug reactions in patients being prescribed carbamazepine for epilepsy is likely to represent a cost-effective use of health care resources [174].

8. Unclear evidence

In some patients treated with VPA, severe hyperammonemia has been observed in the absence of liver failure and may result in encephalopathy with the following symptoms: vomiting, ataxia, behavioural changes, lethargy, somnolence, or, in extreme cases, coma [175]. The exact mechanism of VPA-induced encephalopathy has not been fully defined yet. A prospective multi-center study evaluated the putative association between the T1405 polymorphism in the carbamoyl phosphate synthetase 1 (*CPS1*) gene and occurrence of VPA-induced hyperammonemia in a cohort of 142 adult Caucasian patients with epilepsy treated with valproic acid for at least one year and with normal liver function. They found that this variant was a significant risk factor for the occurrence of hyperammonemia, even in patients with serum VPA levels within a specified therapeutic range [176]. Non-alcoholic fatty liver disease is another adverse reaction that can be induced by VPA treatment [177] and this chronic liver condition is associated with elevated serum levels of γ -glutamyltransferase (γ -GT) [178]. A retrospective study in Japanese patients showed that the Val16Ala polymorphism of the Superoxide Dismutase 2 (*SOD2*) gene, encoding an antioxidant enzyme with a critical role in the detoxification of mitochondrial reactive oxygen species, has an impact on the relationship between VPA exposure and γ -GT elevation. This was determined by using a population pharmacokinetic-pharmacodynamic modelling approach [179]. Weight gain, a common adverse reaction of VPA, has been associated with leptin receptor (*LEPR*) and ankyrin repeat kinase domain containing 1 (*ANKK1*) gene polymorphisms in a cohort of Han Chinese people with epilepsy [180]. All these findings need replication.

Although the mechanism of VPA-induced adverse effects is not clearly understood, there is evidence that its metabolic pattern is associated with the pathogenesis of adverse drug reactions. VPA-induced liver damage has been associated with CYP2C9- and CYP2A6-mediated formation of the hepatotoxic 4-ene metabolite [181]. In a paediatric cohort, Budi et al. [182] found that CYP2C9 variant-guided treatment significantly reduced valproic acid misdosing. In the group of children (n=52) who received a CYP2C9-status adapted dose, signs of toxicity, notably hyperammonemia, were reduced. These findings, as many others in epilepsy pharmacogenetics, still require replication.

There are other studies of genetic factors associated with adverse drug reactions, with unclear evidence. We made an arbitrary selection of some of the most recent or potentially clinically relevant studies. Additional studies can be found listed on the Epilepsy Genetic Association Database (epiGAD; <http://www.epigad.org/>).

A summary of all the findings presented is reported in Table 1.

Table 1

Influence of genetic factors on response and adverse reactions to AEDs through various mediators: summary of existing findings.

Response	Mediator	Genetic factor	Effect [references]
Pharmacokinetics and pharmacodynamics		Variation in <i>CYP2C9</i> gene	Risk of developing concentration-dependent neurotoxicity from phenytoin [12,13]–established evidence
		Variation in <i>CYP2C19</i> gene	Association with the serum concentration of N-desmethyloclobazam and with its clinical efficacy, indicating a gene-dose effect [17–21]
		Variation in <i>CYP2C19</i> gene	Ethnic differences in the tolerability profile of phenobarbital [22]
		<i>UGT1A1</i> variants	Altered clearance of lamotrigine [25]
		Variation in <i>CYP2C19</i> gene	Risk of adverse reactions from zonisamide [28]
		Variation in <i>SCN1A</i> , <i>ABCC2</i> , <i>UGT2B7</i> genes	Association with oxcarbazepine maintenance doses [36]
		Variation in <i>CYP1A1</i> gene	Association with response to first-line antiepileptic drugs in Indian women [37,38]
		<i>ABCB1</i> gene (encoding P-glycoprotein, P-gp, multidrug transporter) variants	Drug-resistant epilepsy [40–45]
		Variation in genes coding for AED targets	No significant association with drug response [49–53]

Table 1 (Continued)

Response		
Mediator	Genetic factor	Effect [references]
Epilepsy genes	Mutations in the <i>SLC2A1</i> gene causing GLUT-1 deficiency syndrome	Gold standard treatment is the ketogenic diet, treating the symptoms of neuroglycopenia [57–59]- established evidence
	Bi-allelic mutations in the <i>ALDH7A1</i> gene causing pyridoxine (vitamin B6)-dependent epilepsy	Gold standard treatment is pyridoxine or pyridoxal 5'-phosphate supplementation [60,61]- established evidence
	<i>SCN1A</i> -related epilepsies	Stiripentol is effective in Dravet Syndrome (especially when combined with valproate and clobazam), established in a randomised controlled trial; however, the use of stiripentol, valproate and clobazam does not always yield complete seizure freedom and may cause adverse side effects [70–72] Ranolazine was identified as a selective blocker of persistent currents in mutant NaV1.1 channels expressed in heterologous expression systems [76–78]- uncertain evidence, recently it was shown that ranolazine does not inhibit the persistent Na ⁺ current more strongly than phenytoin in central neurons Clemizole was identified as an effective inhibitor of spontaneous convulsive behaviour and electrographic seizures in zebrafish Na _v 1.1 (<i>scn1Lab</i>) mutants [81] Fenfluramine has serotonergic effects and was shown to significantly reduce epileptiform discharges in <i>scn1Lab</i> morphants. Evidence of effectiveness in control of convulsive seizures and good tolerability in a small cohort of patients with Dravet Syndrome [83–89]- ongoing clinical trials in Dravet syndrome Use of sodium channel blockers can aggravate seizures in Dravet syndrome. Note, however, that lamotrigine can improve seizure control in some patients with Dravet Syndrome [92,94]
	<i>GRIN2A</i> causing early-onset epileptic encephalopathy	Use of memantine, a N-methyl-D-aspartate (NMDA) receptor antagonist, can inhibit the increased activity of the NMDA receptor caused by specific mutations [102]
	<i>KCNT1</i> -related epilepsy	Use of quinidine, partial antagonist of KCNT1 used as antiarrhythmic drug, was shown to reduce seizure frequency and improve psychomotor development in one patient with migrating partial seizures of infancy [103] and was shown to reverse the hyperactivity of mutant KCNT1 in <i>Xenopus</i> oocytes [104]
	<i>KCNQ2</i> -related epilepsies	Use of retigabine (ezogabine), a positive allosteric modulator of KCNQ2-5 (K _v 7.2–7.5) ion channels, was shown to partially reverse the loss of function, in vitro, of missense <i>KCNQ2</i> mutations associated with severe epileptic encephalopathy [107,108,113]- only preliminary data in humans Sodium channel blockers seem effective in <i>KCNQ2</i> -related epilepsy, possibly because voltage-gated sodium channels and KCNQ potassium channels co-localize and are bound at critical locations of the neuronal membrane [111,114–116]
	<i>SCN2A</i> -related epilepsies	Sodium channel blockers have shown significant effectiveness in <i>SCN2A</i> -epileptic encephalopathies; pathophysiological considerations suggest that sodium channel blockers should only be applied in patients with gain-of-function mutations [118,119] Treatment with oral 5-hydroxytryptophan, L-Dopa/Carbidopa, and a dopa agonist resulted in mild improvement of seizure control, in a case with a de novo <i>SCN2A</i> splice site mutation associated with epileptic encephalopathy [120]
	<i>SCN8A</i> -related epilepsies	Sodium channel blockers have shown effectiveness in patients with gain-of-function mutations; in rare cases an apparent loss-of-function effect has been described but it remains unclear if these may show gain-of-function effect in vivo [121,123,127,128]
	Tuberous sclerosis complex (TSC) associated with <i>TSC1</i> or <i>TSC2</i> mutations	Rapamycin (sirolimus), an inhibitor of the mechanistic target of rapamycin (mTOR) signaling cascade, was shown to prevent the development of epilepsy and premature death in mouse models of TSC and to significantly improve seizure control in children and adults with TSC-associated epilepsy, with a tolerable safety profile [137–141]
	<i>DEPDC5</i> -related epilepsies	<i>DEPDC5</i> encodes a protein that is part of the GATOR1 complex, a negative regulator of the mechanistic target of rapamycin complex 1 (mTORC1), in the mTOR pathway; its mutations are predicted to result in upregulation of the mTOR signaling pathway. Inhibition of mTOR pathway with rapamycin was shown to suppress cytomegalic neurons and epileptic seizures in model systems [152–154]. No studies on treatment with mTOR inhibitors in patients with gene mutations affecting the GATOR1 complex subunit
<i>PRICKLE</i> -mediated seizures	USP9X, a substrate-specific de-ubiquitinase, is a partner in the mammalian PRICKLE-interactome. Inhibition of USP9X can arrest PRICKLE-mediated seizures [163]. No studies in humans	
Adverse reactions	<i>HLA-B*15:02</i>	Stevens-Johnson syndrome and toxic epidermal necrolysis induced by carbamazepine and other aromatic AEDs in patients from Han Chinese and other South Asian ethnic groups [165–170]- established evidence
	<i>HLA-A*31:01</i>	Increased risk of carbamazepine-induced hypersensitivity reactions in patients of European ancestry and in the Japanese population [172,173]- established evidence
	T1405 polymorphism of the <i>CPS1</i> gene	Increased risk of valproate-induced hyperammonaemia in Caucasian patients [176]
	Val16Ala polymorphism of the <i>SOD2</i> gene	Elevated serum level of γ -glutamyltransferase induced by valproate in Japanese patients [179]
	Polymorphic <i>LEPR</i> and <i>ANKK1</i> genes Variation in <i>CYP2C9</i> and <i>CYP2A6</i> genes	Weight gain on valproate in Han Chinese patients [180] Risk of toxicity from valproate [181,182]

8.1. Future of pharmacogenomics: new paradigms for testing and translation?

Recent advances in genetic testing are at the heart of current research on the genetic factors influencing drug response and adverse drug reactions in epilepsy. Genetic, and especially genomic, testing is likely to be increasingly used to improve the effectiveness and safety of epilepsy treatments. Precision medicine treatments represent a new incarnation of the age-old physician's paradigm to consider treatment for each patient holistically: genetics may permit therapy directed at reversing or circumventing the pathophysiological effects of specific gene mutations. Precision medicine could transform clinical care in epilepsy in the form of a new treatment framework and prognostic tools.

A systematic approach to precision medicine in epilepsy should be based on: large cohorts of people with epilepsy with deep genotype-phenotype correlations; standardised functional characterisation of gene mutations which have had frequency and types determined in cases and controls; and the initiation of well-designed innovative clinical trials of targeted treatments identified through functional work. This will require new and more intensive collaborations and integrated research groups that bring together researchers with clinical, genetic, pharmacological and biological expertise.

Funding

We are grateful for support from the Wellcome Trust (Strategic Award, WT104033AIA), the Epilepsy Society, The Muir Maxwell Trust and European Commission FP7 grant award 279062, 'EpiPGX'.

Acknowledgement

This work was undertaken at University College London Hospitals, which received a proportion of funding from the NIHR Biomedical Research Centres funding scheme.

References

- [1] S.L. Moshé, E. Perucca, P. Ryvlin, T. Tomson, Epilepsy: new advances, *Lancet* 385 (2015) 884–898, [http://dx.doi.org/10.1016/S0140-6736\(14\)60456-6](http://dx.doi.org/10.1016/S0140-6736(14)60456-6).
- [2] R. Guerrini, Epilepsy in children, *Lancet* 367 (2006) 499–524, [http://dx.doi.org/10.1016/S0140-6736\(06\)68182-8](http://dx.doi.org/10.1016/S0140-6736(06)68182-8).
- [3] E. Perucca, T. Tomson, The pharmacological treatment of epilepsy in adults, *Lancet Neurol.* 10 (2011) 446–456, [http://dx.doi.org/10.1016/S1474-4422\(11\)70047-3](http://dx.doi.org/10.1016/S1474-4422(11)70047-3).
- [4] P. Striano, S. Striano, C. Minetti, F. Zara, Refractory, life-threatening status epilepticus in a 3-year-old girl, *Lancet Neurol.* 7 (2008) 278–284, [http://dx.doi.org/10.1016/S1474-4422\(08\)70043-7](http://dx.doi.org/10.1016/S1474-4422(08)70043-7).
- [5] M.P. Canevini, G. De Sarro, C.A. Galimberti, G. Gatti, L. Licchetta, A. Malerba, et al., Relationship between adverse effects of antiepileptic drugs, number of coprescribed drugs, and drug load in a large cohort of consecutive patients with drug-refractory epilepsy, *Epilepsia* 51 (2010) 797–804, <http://dx.doi.org/10.1111/j.1528-1167.2010.02520.x>.
- [6] V. Franco, E. Perucca, The pharmacogenomics of epilepsy, *Expert Rev. Neurother.* 15 (2015) 1161–1170, <http://dx.doi.org/10.1586/14737175.2015.1083424>.
- [7] P.S. Reif, M.-H. Tsai, I. Helbig, F. Rosenow, K.M. Klein, Precision medicine in genetic epilepsies: break of dawn? *Expert Rev. Neurother.* (2016) 1–12, <http://dx.doi.org/10.1080/14737175.2017.1253476>.
- [8] W. Löscher, U. Klotz, F. Zimprich, D. Schmidt, The clinical impact of pharmacogenetics on the treatment of epilepsy, *Epilepsia* 50 (2009) 1–23, <http://dx.doi.org/10.1111/j.1528-1167.2008.01716.x>.
- [9] L.E. Walker, N. Mirza, V.L.M. Yip, A.G. Marson, M. Pirmohamed, Personalized medicine approaches in epilepsy, *J. Intern. Med.* 277 (2015) 218–234, <http://dx.doi.org/10.1111/joim.12322>.
- [10] S.M. Sisodiya, C. Marini, Genetics of antiepileptic drug resistance, *Curr. Opin. Neurol.* 22 (2009) 150–156, <http://dx.doi.org/10.1097/WCO.0b013e32832923ec>.
- [11] M.A. Lopez-García, I.A. Fera-Romero, H. Fernando-Serrano, D. Escalante-Santiago, I. Grijalva, S. Orozco-Suarez, Genetic polymorphisms associated with antiepileptic metabolism, *Front. Biosci. (Elite Ed)* 6 (2014) 377–386.
- [12] C.R. Lee, J.A. Goldstein, J.A. Pieper, Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data, *Pharmacogenetics* 12 (2002) 251–263.
- [13] C. Depondt, P. Godard, R.S. Espel, A.L. Da Cruz, P. Lienard, M. Pandolfo, A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity, *Eur. J. Neurol.* 18 (2011) 1159–1164, <http://dx.doi.org/10.1111/j.1468-1331.2011.03361.x>.
- [14] S.K. Tate, C. Depondt, S.M. Sisodiya, G.L. Cavalleri, S. Schorge, N. Soranzo, 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.* 102 (2005) 5507–5512, <http://dx.doi.org/10.1073/pnas.0407346102>.
- [15] W.-H. Chung, W.-C. Chang, Y.-S. Lee, Y.-Y. Wu, C.-H. Yang, H.-C. Ho, et al., Genetic variants associated with phenytoin-related severe cutaneous adverse reactions, *JAMA* 312 (2014) 525–534, <http://dx.doi.org/10.1001/jama.2014.7859>.
- [16] C. Giraud, A. Tran, E. Rey, J. Vincent, J.-M. Tréluyer, G. Pons, In vitro characterization of clobazam metabolism by recombinant cytochrome P450 enzymes: importance of CYP2C19, *Drug Metab. Dispos.* 32 (2004) 1279–1286.
- [17] S.M. De Morais, G.R. Wilkinson, J. Blaisdell, U.A. Meyer, K. Nakamura, J.A. Goldstein, Identification of a new genetic defect responsible for the polymorphism of (S)-mephenytoin metabolism in Japanese, *Mol. Pharmacol.* 46 (1994) 594–598.
- [18] M. Contin, S. Sangiorgi, R. Riva, A. Parmeggiani, F. Albani, A. Baruzzi, Evidence of polymorphic CYP2C19 involvement in the human metabolism of N-desmethylclobazam, *Ther. Drug Monit.* 24 (2002) 737–741.
- [19] K. Kosaki, K. Tamura, R. Sato, H. Samejima, Y. Tanigawara, T. Takahashi, A major influence of CYP2C19 genotype on the steady-state concentration of N-desmethylclobazam, *Brain Dev.* 26 (2004) 530–534, <http://dx.doi.org/10.1016/j.braindev.2004.02.010>.
- [20] T. Seo, R. Nagata, T. Ishitsu, T. Murata, C. Takaishi, M. Hori, et al., Impact of CYP2C19 polymorphisms on the efficacy of clobazam therapy, *Pharmacogenomics* 9 (2008) 527–537, <http://dx.doi.org/10.2217/14622416.9.5.527>.
- [21] S. Hashi, I. Yano, M. Shibata, S. Masuda, M. Kinoshita, R. Matsumoto, et al., Effect of CYP2C19 polymorphisms on the clinical outcome of low-dose clobazam therapy in Japanese patients with epilepsy, *Eur. J. Clin. Pharmacol.* 71 (2015) 51–58, <http://dx.doi.org/10.1007/s00228-014-1773-z>.
- [22] S. Goto, T. Seo, T. Murata, N. Nakada, N. Ueda, T. Ishitsu, et al., Population estimation of the effects of cytochrome P450 2C9 and 2C19 polymorphisms on phenobarbital clearance in Japanese, *Ther. Drug Monit.* 29 (2007) 118–121, <http://dx.doi.org/10.1097/FTD.0b013e318030def0>.
- [23] Chemistry and biotransformation, 1999 47–75.
- [24] T.K.L. Kiang, P.C. Ho, M.R. Anari, V. Tong, F.S. Abbott, T.K.H. Chang, Contribution of CYP2C9, CYP2A6, and CYP2B6 to valproic acid metabolism in hepatic microsomes from individuals with the CYP2C9*1/*1 genotype, *Toxicol. Sci.* 94 (2006) 261–271, <http://dx.doi.org/10.1093/toxsci/ktl096>.
- [25] J. Posner, A.F. Cohen, G. Land, C. Winton, A.W. Peck, The pharmacokinetics of lamotrigine (BW430C) in healthy subjects with unconjugated hyperbilirubinaemia (Gilbert's syndrome), *Br. J. Clin. Pharmacol.* 28 (1989) 117–120.
- [26] M. Baulac, Introduction to zonisamide, *Epilepsy Res.* 68 (Suppl. (2)) (2006) S3–S9, <http://dx.doi.org/10.1016/j.eplepsyres.2005.11.004>.
- [27] H. Nakasa, H. Nakamura, S. Ono, M. Tsutsui, M. Kiuchi, S. Ohmori, et al., Prediction of drug–drug interactions of zonisamide metabolism in humans from in vitro data, *Eur. J. Clin. Pharmacol.* 54 (1998) 177–183.
- [28] Y. Okada, T. Seo, T. Ishitsu, A. Waniibuchi, N. Hashimoto, Y. Higa, et al., Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance, *Ther. Drug Monit.* 30 (2008) 540–543, <http://dx.doi.org/10.1097/FTD.0b013e31817d842a>.
- [29] M. Eichelbaum, T. Tomson, G. Tybring, L. Bertilsson, Carbamazepine metabolism in man. Induction and pharmacogenetic aspects, *Clin. Pharmacokinet.* 10 (1985) 80–90, <http://dx.doi.org/10.2165/00003088-198510010-00004>.
- [30] K. Klein, M. Thomas, S. Winter, A.K. Nussler, M. Niemi, M. Schwab, et al., PPARA: a novel genetic determinant of CYP3A4 in vitro and in vivo, *Clin. Pharmacol. Ther.* 91 (2012) 1044–1052, <http://dx.doi.org/10.1038/clpt.2011.336>.
- [31] P. Kang, M. Liao, M.R. Wester, J.S. Leeder, R.E. Pearce, M.A. Correia, CYP3A4-mediated carbamazepine (CBZ) metabolism: formation of a covalent CBZ-CYP3A4 adduct and alteration of the enzyme kinetic profile, *Drug Metab. Dispos.* 36 (2008) 490–499, <http://dx.doi.org/10.1124/dmd.107.016501>.
- [32] R.E. Pearce, G.R. Vakkalagadda, J.S. Leeder, Pathways of carbamazepine bioactivation in vitro I. Characterization of human cytochromes P450 responsible for the formation of 2- and 3-hydroxylated metabolites, *Drug Metab. Dispos.* 30 (2002) 1170–1179.
- [33] W. Yun, F. Zhang, C. Hu, X. Luo, P. Xue, J. Wang, et al., Effects of EPHX1, SCN1A and CYP3A4 genetic polymorphisms on plasma carbamazepine concentrations and pharmacoresistance in Chinese patients with epilepsy, *Epilepsy Res.* 107 (2013) 231–237, <http://dx.doi.org/10.1016/j.eplepsyres.2013.09.011>.
- [34] A. Daci, G. Beretta, D. Villasali, A. Shala, V. Govori, G.D. Norata, 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* 10 (2015) e0142408, <http://dx.doi.org/10.1371/journal.pone.0142408>.
- [35] R. Hermann, J. Borlak, U. Munzel, G. Niebch, U. Fuhr, J. Maus, et al., The role of Gilbert's syndrome and frequent NAT2 slow acetylation polymorphisms in the pharmacokinetics of retigabine, *Pharmacogenomics J.* 6 (2006) 211–219, <http://dx.doi.org/10.1038/sj.tpj.6500359>.
- [36] C.-L. Ma, X.-Y. Wu, Z. Jiao, Z. Hong, Z.-Y. Wu, M.-K. Zhong, SCN1A, ABC2 and UGT2B7 gene polymorphisms in association with individualized oxcarbazepine therapy, *Pharmacogenomics* 16 (2015) 347–360, <http://dx.doi.org/10.2217/pgs.14.186>.
- [37] S. Grover, P. Talwar, M. Gourie-Devi, M. Gupta, K. Bala, S. Sharma, et al., Genetic polymorphisms in sex hormone metabolizing genes and drug response in women with epilepsy, *Pharmacogenomics* 11 (2010) 1525–1534, <http://dx.doi.org/10.2217/pgs.10.120>.
- [38] P. Talwar, N. Kanodia, S. Mahendru, R. Baghel, S. Grover, G. Arora, et al., Genetic contribution of CYP1A1 variant on treatment outcome in epilepsy patients: a functional and interethnic perspective, *Pharmacogenomics J.* (2016), <http://dx.doi.org/10.1038/tpj.2016.1>.
- [39] S. Dallas, D.S. Miller, R. Bendayan, Multidrug resistance-associated proteins: expression and function in the central nervous system, *Pharmacol. Rev.* 58 (2006) 140–161, <http://dx.doi.org/10.1124/pr.58.2.3>.
- [40] H. Potschka, M.J. Brodie, Pharmacoresistance, *Handb. Clin. Neurol.* 108 (2012) 741–757, <http://dx.doi.org/10.1016/B978-0-444-52899-5.00025-3>.
- [41] A. Siddiqui, R. Kerb, M.E. Weale, U. Brinkmann, A. Smith, D.B. Goldstein, et al., Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1, *N. Engl. J. Med.* 348 (2003) 1442–1448, <http://dx.doi.org/10.1056/NEJMoa021986>.
- [42] F.G. Bourmissen, M.E. Moretti, D.N. Juurlink, G. Koren, M. Walker, Y. Finkelstein, Polymorphism of the MDR1/ABCB1 C3435T drug-transporter and resistance to anticonvulsant drugs: a meta-analysis, *Epilepsia* 50 (2009) 898–903, <http://dx.doi.org/10.1111/j.1528-1167.2008.01858.x>.
- [43] B.S. Haerian, K.S. Lim, C.T. Tan, A.A. Raymond, Z. Mohamed, Association of ABCB1 gene polymorphisms and their haplotypes with response to antiepileptic drugs: a systematic review and meta-analysis, *Pharmacogenomics* 12 (2011) 713–725, <http://dx.doi.org/10.2217/pgs.10.212>.
- [44] I. Manna, A. Gambardella, A. Labate, L. Mumoli, Polymorphism of the multidrug resistance 1 gene MDR1/ABCB1 C3435T and response to antiepileptic drug treatment in temporal lobe epilepsy, *Seizure* (2015).
- [45] S.-X. Li, Y.-Y. Liu, Q.-B. Wang, ABCB1 gene C3435T polymorphism and drug resistance in epilepsy: evidence based on 8 604 subjects, *Med. Sci. Monit.* 21 (2015) 861–868, <http://dx.doi.org/10.12659/MSM.894023>.
- [46] C. Simon, B. Stieger, G.A. Kullak-Ublick, M. Fried, S. Mueller, J.-M. Fritschy, et al., Intestinal expression of cytochrome P450 enzymes and ABC transporters and carbamazepine and phenytoin disposition, *Acta Neurol. Scand.* 115 (2007) 232–242, <http://dx.doi.org/10.1111/j.1600-0404.2006.00761.x>.
- [47] D.W. Kim, S.K. Lee, K. Chu, I.-J. Jang, K.-S. Yu, J.-Y. Cho, et al., Lack of association between ABCB1, ABCG2, and ABC2 genetic polymorphisms and multidrug resistance in partial epilepsy, *Epilepsy Res.* 84 (2009) 86–90, <http://dx.doi.org/10.1016/j.eplepsyres.2008.12.001>.
- [48] M. Ufer, I. Mosyagin, H. Muhle, T. Jacobsen, S. Haenisch, R. Häslar, et al., Non-response to antiepileptic pharmacotherapy is associated with the ABCG2 –24C > T polymorphism in young and adult patients with epilepsy, *Pharmacogenet. Genomics* 19 (2009) 353–362.
- [49] B.S. Haerian, L. Baum, P. Kwan, H.J. Tan, A.A. Raymond, Z. Mohamed, SCN1A, SCN2A and SCN3A gene polymorphisms and responsiveness to antiepileptic drugs: a multicenter cohort study and meta-analysis, *Pharmacogenomics* 14 (2013) 1153–1166, <http://dx.doi.org/10.2217/pgs.13.104>.
- [50] J. Qu, Y. Zhang, Z.-Q. Yang, X.-Y. Mao, B.-T. Zhou, J.-Y. Yin, 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.* 20 (2014) 140–146, <http://dx.doi.org/10.1111/cns.12169>.
- [51] B.-T. Zhou, Q.-H. Zhou, J.-Y. Yin, G.-L. Li, J. Qu, X.-J. Xu, 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.* 18 (2012) 566–572, <http://dx.doi.org/10.1111/j.1755-5949.2012.00321.x>.
- [52] J.M. Lynch, S.K. Tate, P. Kinirons, M.E. Weale, G.L. Cavalleri, C. Depondt, et al., No major role of common SV2A variation for predisposition or levetiracetam response in epilepsy, *Epilepsy Res.* 83 (2009) 44–51, <http://dx.doi.org/10.1016/j.eplepsyres.2008.09.003>.
- [53] C. Piana, N. de J. Antunes, O. Della Pasqua, Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs, *Expert Opin. Drug Metab. Toxicol.* 10 (2014) 341–358, <http://dx.doi.org/10.1517/17425255.2014.872630>.
- [54] M. Pirmohamed, Personalized pharmacogenomics: predicting efficacy and adverse drug reactions, *Annu. Rev. Genomics Hum. Genet.* 15 (2014) 349–370, <http://dx.doi.org/10.1146/annurev-genom-090413-025419>.
- [55] L.R. Cardon, T. Harris, Precision medicine, genomics and drug discovery, *Hum. Mol. Genet.* 25 (2016) R166–R172, <http://dx.doi.org/10.1093/hmg/ddw246>.
- [56] R. Valdes, D.T. Yin, Fundamentals of pharmacogenetics in personalized, precision medicine, *Clin. Lab. Med.* 36 (2016) 447–459, <http://dx.doi.org/10.1016/j.cll.2016.05.006>.
- [57] D.C. De Vivo, L. Leary, D. Wang, Glucose transporter 1 deficiency syndrome and other glycolytic defects, *J. Child Neurol.* 17 (Suppl. (3)) (2002), 3515–23–discussion 3524–5.
- [58] A.W. Pong, B.R. Geary, K.M. Engelstad, A. Natarajan, H. Yang, D.C. De Vivo, Glucose transporter type I deficiency syndrome: epilepsy phenotypes and outcomes, *Epilepsia* 53 (2012) 1503–1510, <http://dx.doi.org/10.1111/j.1528-1167.2012.03592.x>.
- [59] V. De Giorgis, P. Veggiotti, GLUT1 deficiency syndrome 2013: current state of the art, *Seizure* 22 (2013) 803–811, <http://dx.doi.org/10.1016/j.seizure.2013.07.003>.
- [60] P.B. Mills, E. Struys, C. Jakobs, B. Plecko, P. Baxter, M. Baumgartner, et al., Mutations in antiquitin in individuals with pyridoxine-dependent seizures, *Nat. Med.* 12 (2006) 307–309, <http://dx.doi.org/10.1038/nm1366>.
- [61] P.B. Mills, S.S.M. Camuzeaux, E.J. Footitt, K.A. Mills, P. Gissen, L. Fisher, et al., Epilepsy due to PNPO mutations: genotype, environment and treatment affect presentation and outcome, *Brain* 137 (2014) 1350–1360, <http://dx.doi.org/10.1093/brain/awu051>.
- [62] B.P.G.M. Ceulemans, L.R.F. Claes, L.G. Lagae, Clinical correlations of mutations in the SCN1A gene: from febrile seizures to severe myoclonic epilepsy in infancy, *Pediatr. Neurol.* 30 (2004) 236–243, <http://dx.doi.org/10.1016/j.pediatrneurol.2003.10.012>.
- [63] A.M. De Stasi, P. Farisello, I. Marcon, S. Cavallari, A. Forli, D. Vecchia, et al., Unaltered network activity and interneuronal firing during spontaneous cortical dynamics in vivo in a mouse model of severe myoclonic epilepsy of infancy, *Cereb. Cortex.* 26 (2016) 1778–1794, <http://dx.doi.org/10.1093/cercor/bhw002>.
- [64] Y. Sun, S.P. Pasca, T. Portmann, C. Gool, K.A. Worringer, W. Guan, et al., A deleterious Nav1.1 mutation selectively impairs telencephalic inhibitory neurons derived from Dravet Syndrome patients, *Elife* 5 (479) (2016), <http://dx.doi.org/10.7554/elife.13073>.
- [65] F.H. Yu, M. Mantegazza, R.E. Westenbroek, C.A. Robbins, F. Kalume, K.A. Burton, et al., Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy, *Nat. Neurosci.* 9 (2006) 1142–1149, <http://dx.doi.org/10.1038/nn1754>.
- [66] Y. Liu, L.F. Lopez-Santiago, Y. Yuan, J.M. Jones, H. Zhang, H.A. O'Malley, et al., Dravet syndrome patient-derived neurons suggest a novel epilepsy mechanism, *Ann. Neurol.* 74 (2013) 128–139, <http://dx.doi.org/10.1002/ana.23897>.
- [67] P. Kurbatova, F. Wendling, A. Kaminska, A. Rosati, R. Nabbut, R. Guerrini, et al., Dynamic changes of depolarizing GABA in a computational model of epileptogenic brain: insight for Dravet syndrome, *Exp. Neurol.* 283 (2016) 57–72, <http://dx.doi.org/10.1016/j.expneurol.2016.05.037>.
- [68] J. Hsiao, T.Y. Yuan, M.S. Tsai, C.Y. Lu, Y.C. Lin, M.L. Lee, et al., Upregulation of haploinsufficient gene expression in the brain by targeting a long non-coding RNA improves seizure phenotype in a model of dravet syndrome, *EBioMedicine* 9 (2016) 257–277, <http://dx.doi.org/10.1016/j.ebiom.2016.05.011>.
- [69] F. Brigo, S.C. Igwe, Antiepileptic drugs for the treatment of infants with severe myoclonic epilepsy, *Cochrane Database Syst. Rev.* (2015) CD010483, <http://dx.doi.org/10.1002/14651858.cd010483.pub3>.
- [70] C. Chiron, M.C. Marchand, A. Tran, E. Rey, P. d'Athis, J. Vincent, et al., Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group, *Lancet* 356 (2000) 1638–1642.
- [71] J. Perez, C. Chiron, C. Musial, E. Rey, H. Blehaut, P. d'Athis, et al., Stiripentol: efficacy and tolerability in children with epilepsy, *Epilepsia* 40 (1999) 1618–1626.
- [72] S. Balestrini, S.M. Sisodiya, Audit of use of stiripentol in adults with Dravet syndrome, *Acta Neurol. Scand.* (2016), <http://dx.doi.org/10.1111/ane.12611>.
- [73] S.S. Schutte, R.J. Schutte, E.V. Barragan, D.K. O'Dowd, Model systems for studying cellular mechanisms of SCN1A-related epilepsy, *J. Neurophysiol.* 115 (2016) 1755–1766, <http://dx.doi.org/10.1152/jn.00824.2015>.
- [74] A. Escayg, A.L. Goldin, Sodium channel SCN1A and epilepsy: mutations and mechanisms, *Epilepsia* 51 (2010) 1650–1658, <http://dx.doi.org/10.1111/j.1528-1167.2010.02640.x>.
- [75] G. Bechi, R. Rusconi, S. Cestè, P. Striano, S. Franceschetti, M. Mantegazza, Rescuable folding defective Nav1.1 (SCN1A) mutants in epilepsy: properties, occurrence, and novel rescuing strategy with peptides targeted to the endoplasmic reticulum, *Neurobiol. Dis.* 75 (2015) 100–114, <http://dx.doi.org/10.1016/j.nbd.2014.12.028>.
- [76] K.M. Kahlig, I. Lepist, K. Leung, S. Rajamani, A.L. George, Ranolazine selectively blocks persistent current evoked by epilepsy-associated Nav1.1 mutations, *Br. J. Pharmacol.* 161 (2010) 1414–1426, <http://dx.doi.org/10.1111/j.1476-5381.2010.00976.x>.
- [77] K.M. Kahlig, R. Hirakawa, L. Liu, A.L. George, L. Belardinelli, S. Rajamani, Ranolazine reduces neuronal excitability by interacting with inactivated states of brain sodium channels, *Mol. Pharmacol.* 85 (2014) 162–174, <http://dx.doi.org/10.1124/mol.113.088492>.
- [78] B. Terragni, P. Scalmani, E. Colombo, S. Franceschetti, M. Mantegazza, Ranolazine vs phenytoin: greater effect of ranolazine on the transient Na(+) current than on the persistent Na(+) current in central neurons, *Neuropharmacology* 110 (2016) 223–236, <http://dx.doi.org/10.1016/j.neuropharm.2016.06.029>.
- [79] C.H. Thompson, K.M. Kahlig, A.L. George, SCN1A splice variants exhibit divergent sensitivity to commonly used antiepileptic drugs, *Epilepsia* 52 (2011) 1000–1009, <http://dx.doi.org/10.1111/j.1528-1167.2011.03040.x>.

- [80] A.M. Mistry, C.H. Thompson, A.R. Miller, C.G. Vanoye, A.L. George, J.A. Kearney, Strain- and age-dependent hippocampal neuron sodium currents correlate with epilepsy severity in Dravet syndrome mice, *Neurobiol. Dis.* 65 (2014) 1–11, <http://dx.doi.org/10.1016/j.nbd.2014.01.006>.
- [81] S.C. Baraban, M.T. Dinday, G.A. Hortopan, Drug screening in *Scn1a* zebrafish mutant identifies clemizole as a potential Dravet syndrome treatment, *Nat. Commun.* 4 (2410) (2013), <http://dx.doi.org/10.1038/ncomms3410>.
- [82] P.J. Schoonheim, A.B. Arrenberg, F. Del Bene, H. Baier, Optogenetic localization and genetic perturbation of saccade-generating neurons in zebrafish, *J. Neurosci.* 30 (2010) 7111–7120, <http://dx.doi.org/10.1523/JNEUROSCI.5193-09.2010>.
- [83] B. Ceulemans, M. Boel, K. Leyssens, C. Van Rossem, P. Neels, P.G. Jorens, et al., Successful use of fenfluramine as an add-on treatment for Dravet syndrome, *Epilepsia* 53 (2012) 1131–1139, <http://dx.doi.org/10.1111/j.1528-1167.2012.03495.x>.
- [84] B. Ceulemans, A.-S. Schoonjans, F. Marchau, B.P. Paelinck, L. Lagae, Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine, *Epilepsia* 57 (2016) e129–e134, <http://dx.doi.org/10.1111/epi.13407>.
- [85] U.D. McCann, L.S. Seiden, L.J. Rubin, G.A. Ricaurte, Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine. A systematic review of the evidence, *JAMA* 278 (1997) 666–672.
- [86] C.F. Dahl, M.R. Allen, P.M. Urie, P.N. Hopkins, Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals, *BMC Med.* 6 (34) (2008), <http://dx.doi.org/10.1186/1741-7015-6-34>.
- [87] R.W. Fuller, H.D. Snoddy, D.W. Robertson, Mechanisms of effects of d-fenfluramine on brain serotonin metabolism in rats: uptake inhibition versus release, *Pharmacol. Biochem. Behav.* 30 (1988) 715–721.
- [88] M.T. Dinday, S.C. Baraban, Large-scale phenotype-based antiepileptic drug screening in a zebrafish model of dravet syndrome(1,2,3), *eNeuro* 2 (2015), <http://dx.doi.org/10.1523/ENEURO.0068-15.2015>.
- [89] Y. Zhang, A. Kecskés, D. Copmans, M. Langlois, A.D. Crawford, B. Ceulemans, et al., Pharmacological characterization of an antisense knockdown zebrafish model of Dravet syndrome: inhibition of epileptic seizures by the serotonin agonist fenfluramine, *PLoS One* 10 (2015) e0125898, <http://dx.doi.org/10.1371/journal.pone.0125898>.
- [90] B.P. Guiard, G. Di Giovanni, Central serotonin-2A (5-HT_{2A}) receptor dysfunction in depression and epilepsy: the missing link? *Front. Pharmacol.* 6 (46) (2015), <http://dx.doi.org/10.3389/fphar.2015.00046>.
- [91] J. Sourbron, H. Schneider, A. Kecskés, Y. Liu, E.M. Buening, L. Lagae, et al., Serotonergic modulation as effective treatment for dravet syndrome in a zebrafish mutant model, *ACS Chem. Neurosci.* 7 (2016) 588–598, <http://dx.doi.org/10.1021/acscchemneuro.5b00342>.
- [92] A. Brunklaus, R. Ellis, E. Reavey, G.H. Forbes, S.M. Zuberi, Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome, *Brain* 135 (2012) 2329–2336, <http://dx.doi.org/10.1093/brain/aws151>.
- [93] B. Tang, K. Dutt, L. Papale, R. Rusconi, A. Shankar, J. Hunter, et al., A BAC transgenic mouse model reveals neuron subtype-specific effects of a Generalized Epilepsy with Febrile Seizures Plus (GEFS+) mutation, *Neurobiol. Dis.* 35 (2009) 91–102, <http://dx.doi.org/10.1016/j.nbd.2009.04.007>.
- [94] L. Dalic, S.A. Mullen, E. Roulet Perez, I. Scheffer, Lamotrigine can be beneficial in patients with Dravet syndrome, *Dev. Med. Child Neurol.* 57 (2015) 200–202, <http://dx.doi.org/10.1111/dmcn.12593>.
- [95] G. Bechi, P. Scalmani, E. Schiavon, R. Rusconi, S. Franceschetti, M. Mantegazza, Pure haploinsufficiency for Dravet syndrome Na(V)1.1 (SCN1A) sodium channel truncating mutations, *Epilepsia* 53 (2012) 87–100, <http://dx.doi.org/10.1111/j.1528-1167.2011.03346.x>.
- [96] S. Endele, G. Rosenberger, K. Geider, B. Popp, C. Tamer, I. Stefanova, et al., Mutations in GRIN2A and GRIN2B encoding regulatory subunits of NMDA receptors cause variable neurodevelopmental phenotypes, *Nat. Genet.* 42 (2010) 1021–1026, <http://dx.doi.org/10.1038/ng.677>.
- [97] J. de Ligt, M.H. Willemsen, B.W.M. van Bon, T. Kleefstra, H.G. Yntema, T. Kroes, et al., Diagnostic exome sequencing in persons with severe intellectual disability, *N. Engl. J. Med.* 367 (2012) 1921–1929, <http://dx.doi.org/10.1056/NEJMoa1206524>.
- [98] G.L. Carvill, B.M. Regan, S.C. Yendle, B.J. O’Roak, N. Lozovaya, N. Bruneau, et al., GRIN2A mutations cause epilepsy-aphasia spectrum disorders, *Nat. Genet.* 45 (2013) 1073–1076, <http://dx.doi.org/10.1038/ng.2727>.
- [99] J.R. Lemke, D. Lal, E.M. Reinthaler, I. Steiner, M. Nothnagel, M. Alber, et al., Mutations in GRIN2A cause idiopathic focal epilepsy with rolandic spikes, *Nat. Genet.* 45 (2013) 1067–1072, <http://dx.doi.org/10.1038/ng.2728>.
- [100] G. Lesca, G. Rudolf, N. Bruneau, N. Lozovaya, A. Labalme, N. Boutry-Kryza, et al., GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction, *Nat. Genet.* 45 (2013) 1061–1066, <http://dx.doi.org/10.1038/ng.2726>.
- [101] H. Yuan, K.B. Hansen, J. Zhang, T.M. Pierson, T.C. Markello, K.V.F. Fajardo, et al., Functional analysis of a de novo GRIN2A missense mutation associated with early-onset epileptic encephalopathy, *Nat. Commun.* 5 (2014) 3251, <http://dx.doi.org/10.1038/ncomms4251>.
- [102] T.M. Pierson, H. Yuan, E.D. Marsh, K. Fuentes-Fajardo, D.R. Adams, T. Markello, et al., GRIN2A mutation and early-onset epileptic encephalopathy: personalized therapy with memantine, *Ann. Clin. Transl. Neurol.* 1 (2014) 190–198, <http://dx.doi.org/10.1002/acn3.39>.
- [103] D. Bearden, A. Strong, J. Ehnott, M. DiGiovine, D. Dlugos, E.M. Goldberg, Targeted treatment of migrating partial seizures of infancy with quinidine, *Ann. Neurol.* 76 (2014) 457–461, <http://dx.doi.org/10.1002/ana.24229>.
- [104] R.S. Møller, S.E. Heron, L.H.G. Larsen, C.X. Lim, M.G. Ricos, M.A. Bayly, et al., Mutations in KCNT1 cause a spectrum of focal epilepsies, *Epilepsia* 56 (2015) e114–20, <http://dx.doi.org/10.1111/epi.13071>.
- [105] M.A. Mikati, Y.-H. Jiang, M. Carboni, V. Shashi, S. Petrovski, R. Spillmann, et al., Quinidine in the treatment of KCNT1-positive epilepsies, *Ann. Neurol.* 78 (2015) 995–999, <http://dx.doi.org/10.1002/ana.24520>.
- [106] R. Sachdeo, A. Partiot, V. Biton, W.E. Rosenfeld, V. Nohria, D. Tompson, et al., A novel design for a dose finding, safety, and drug interaction study of an antiepileptic drug (retigabine) in early clinical development, *Int. J. Clin. Pharmacol. Ther.* 52 (2014) 509–518, <http://dx.doi.org/10.5414/CP202081>.
- [107] A. Schenzer, T. Friedrich, M. Pusch, P. Saftig, T.J. Jentsch, J. Grötzinger, et al., Molecular determinants of KCNQ (Kv7) K⁺ channel sensitivity to the anticonvulsant retigabine, *J. Neurosci.* 25 (2005) 5051–5060, <http://dx.doi.org/10.1523/JNEUROSCI.0128-05.2005>.
- [108] T.V. Wuttke, G. Seebohm, S. Bail, S. Maljevic, H. Lerche, The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (KCNQ2) channel by binding to its activation gate, *Mol. Pharmacol.* 67 (2005) 1009–1017, <http://dx.doi.org/10.1124/mol.104.010793>.
- [109] F. Zara, N. Specchio, P. Striano, A. Robbiano, E. Gennaro, R. Paravidino, et al., Genetic testing in benign familial epilepsies of the first year of life: clinical and diagnostic significance, *Epilepsia* 54 (2013) 425–436, <http://dx.doi.org/10.1111/epi.12089>.
- [110] S. Weckhuysen, S. Mandelstam, A. Suls, D. Audenaert, T. Deconinck, L.R.F. Claes, et al., KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy, *Ann. Neurol.* 71 (2012) 15–25, <http://dx.doi.org/10.1002/ana.22644>.
- [111] A.L. Numis, M. Angriman, J.E. Sullivan, A.J. Lewis, P. Striano, R. Nabbout, et al., KCNQ2 encephalopathy: delineation of the electroclinical phenotype and treatment response, *Neurology* 82 (2014) 368–370, <http://dx.doi.org/10.1212/WNL.0000000000000060>.
- [112] G. Orhan, M. Bock, D. Schepers, E.I. Ilina, S.N. Reichel, H. Löffler, et al., Dominant-negative effects of KCNQ2 mutations are associated with epileptic encephalopathy, *Ann. Neurol.* 75 (2014) 382–394, <http://dx.doi.org/10.1002/ana.24080>.
- [113] J.J. Millichap, K.L. Park, T. Tsuchida, B. Ben-Zeev, L. Carmant, R. Flamini, et al., KCNQ2 encephalopathy: features, mutational hot spots, and ezogabine treatment of 11 patients, *Neur. Genet.* 2 e96 (2016), <http://dx.doi.org/10.1212/NXG.0000000000000096>.
- [114] M. Kato, T. Yamagata, M. Kubota, H. Arai, S. Yamashita, T. Nakagawa, et al., Clinical spectrum of early onset epileptic encephalopathies caused by KCNQ2 mutation, *Epilepsia* 54 (2013) 1282–1287, <http://dx.doi.org/10.1111/epi.12200>.
- [115] Z. Pan, T. Kao, Z. Horvath, J. Lemos, J.-Y. Sul, S.D. Cranstoun, et al., A common ankyrin-G-based mechanism retains KCNQ and NaV channels at electrically active domains of the axon, *J. Neurosci.* 26 (2006) 2599–2613, <http://dx.doi.org/10.1523/JNEUROSCI.4314-05.2006>.
- [116] T. Pisano, A.L. Numis, S.B. Heavin, S. Weckhuysen, M. Angriman, A. Suls, et al., Early and effective treatment of KCNQ2 encephalopathy, *Epilepsia* 56 (2015) 685–691, <http://dx.doi.org/10.1111/epi.12984>.
- [117] S.E. Heron, K.M. Crossland, E. Andermann, H.A. Phillips, A.J. Hall, A. Bleasel, et al., Sodium-channel defects in benign familial neonatal-infantile seizures, *Lancet* 360 (2002) 851–852, [http://dx.doi.org/10.1016/S0140-6736\(02\)09968-3](http://dx.doi.org/10.1016/S0140-6736(02)09968-3).
- [118] K. Nakamura, M. Kato, H. Osaka, S. Yamashita, E. Nakagawa, K. Haginoya, et al., Clinical spectrum of SCN2A mutations expanding to Ohtahara syndrome, *Neurology* 81 (2013) 992–998, <http://dx.doi.org/10.1212/WNL.0b013e3182a43e57>.
- [119] K.B. Howell, J.M. McMahon, G.L. Carvill, D. Tambunan, M.T. Mackay, V. Rodriguez-Casero, et al., SCN2A encephalopathy: a major cause of epilepsy of infancy with migrating focal seizures, *Neurology* 85 (2015) 958–966, <http://dx.doi.org/10.1212/WNL.0000000000001926>.
- [120] G.A. Horvath, M. Demos, C. Shyr, A. Matthews, L. Zhang, S. Race, et al., Secondary neurotransmitter deficiencies in epilepsy caused by voltage-gated sodium channelopathies: a potential treatment target? *Mol. Genet. Metab.* 117 (2016) 42–48, <http://dx.doi.org/10.1016/j.ymgme.2015.11.008>.
- [121] J.L. Wagnon, M.H. Meisler, Recurrent and non-Recurrent mutations of SCN8A in epileptic encephalopathy, *Front. Neurol.* 6 (104) (2015), <http://dx.doi.org/10.3389/fneur.2015.00104>.
- [122] Epi4K Consortium, Epilepsy Phenome/Genome Project, A.S., Allen, S.F., Berkovic, P., Cossette, N. Delanty, et al., De novo mutations in epileptic encephalopathies, *Nature*. 501 (2013) 217–221, <http://dx.doi.org/10.1038/nature12439>.
- [123] J. Larsen, G.L. Carvill, E. Gardella, G. Kluger, G. Schmiedel, N. Barisic, et al., The phenotypic spectrum of SCN8A encephalopathy, *Neurology* 84 (2015) 480–489, <http://dx.doi.org/10.1212/WNL.0000000000001211>.
- [124] K.R. Veeramah, J.E. O’Brien, M.H. Meisler, X. Cheng, S.D. Dib-Hajj, S.G. Waxman, et al., De novo pathogenic SCN8A mutation identified by whole-genome sequencing of a family quartet affected by infantile epileptic encephalopathy and SUDEP, *Am. J. Hum. Genet.* 90 (2012) 502–510, <http://dx.doi.org/10.1016/j.ajhg.2012.01.006>.
- [125] C.R. Frasier, J.L. Wagnon, Y.O. Bao, L.G. McVeigh, L.F. Lopez-Santiago, M.H. Meisler, et al., Cardiac arrhythmia in a mouse model of sodium channel

- SCN8A epileptic encephalopathy, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) 12838–12843, <http://dx.doi.org/10.1073/pnas.1612746113>.
- [126] N. Trump, A. McTague, H. Brittain, A. Papandreou, E. Meyer, A. Ngoh, et al., Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis, J. Med. Genet. 53 (2016) 310–317, <http://dx.doi.org/10.1136/jmedgenet-2015-103263>.
- [127] R.S. Boerma, K.P. Braun, M.P.H. van den Broek, M.P.H. van de Broek, F.M.C. van Berkestijn, M.E. Swinkels, et al., Remarkable phenytoin sensitivity in 4 children with SCN8A-related epilepsy: a molecular neuropharmacological approach, Neurotherapeutics 13 (2016) 192–197, <http://dx.doi.org/10.1007/s13311-015-0372-8>.
- [128] B.S. Barker, M. Ottolini, J.L. Wagnon, R.M. Hollander, M.H. Meisler, M.K. Patel, The SCN8A encephalopathy mutation p.Ile1327Val displays elevated sensitivity to the anticonvulsant phenytoin, Epilepsia 57 (2016) 1458–1466, <http://dx.doi.org/10.1111/epi.13461>.
- [129] O. Sancak, M. Nellist, M. Goedbloed, P. Elfferich, C. Wouters, A. Maat-Kievit, et al., Mutational analysis of the TSC1 and TSC2 genes in a diagnostic setting: genotype-phenotype correlations and comparison of diagnostic DNA techniques in Tuberous Sclerosis Complex, Eur. J. Hum. Genet. 13 (2005) 731–741, <http://dx.doi.org/10.1038/sj.ejhg.5201402>.
- [130] D.J. Kwiatkowski, B.D. Manning, Tuberous sclerosis: a GAP at the crossroads of multiple signaling pathways, Hum. Mol. Genet. 14 (2005) R251–R258, <http://dx.doi.org/10.1093/hmg/ddi260> (Sec2).
- [131] D.M. Sabatini, mTOR and cancer: insights into a complex relationship, Nat. Rev. Cancer. 6 (2006) 729–734, <http://dx.doi.org/10.1038/nrc1974>.
- [132] C.J. Chu-Shore, P. Major, S. Camposano, D. Muzykewicz, E.A. Thiele, The natural history of epilepsy in tuberous sclerosis complex, Epilepsia 51 (2010) 1236–1241, <http://dx.doi.org/10.1111/j.1528-1167.2009.02474.x>.
- [133] J.J. Bissler, F.X. McCormack, L.R. Young, J.M. Elwing, G. Chuck, J.M. Leonard, et al., Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangiomyomatosis, N. Engl. J. Med. 358 (2008) 140–151, <http://dx.doi.org/10.1056/NEJMoa063564>.
- [134] S.L. Dabora, D.N. Franz, S. Ashwal, A. Sagalowsky, F.J. DiMario, D. Miles, et al., Multicenter phase 2 trial of sirolimus for tuberous sclerosis: kidney angiomyolipomas and other tumors regress and VEGF-D levels decrease, PLoS One 6 (2011) e23379, <http://dx.doi.org/10.1371/journal.pone.0023379>.
- [135] D.A. Krueger, M.M. Care, K. Holland, K. Agricola, C. Tudor, P. Mangeshkar, et al., Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis, N. Engl. J. Med. 363 (2010) 1801–1811, <http://dx.doi.org/10.1056/NEJMoa1001671>.
- [136] D.N. Franz, K. Agricola, M. Mays, C. Tudor, M.M. Care, K. Holland-Bouley, et al., Everolimus for subependymal giant cell astrocytoma: 5-year final analysis, Ann. Neurol. 78 (2015) 929–938, <http://dx.doi.org/10.1002/ana.24523>.
- [137] L. Meikle, K. Pollizzi, A. Egnor, I. Kramvis, H. Lane, M. Sahin, et al., Response of a neuronal model of tuberous sclerosis to mammalian target of rapamycin (mTOR) inhibitors: effects on mTORC1 and Akt signaling lead to improved survival and function, J. Neurosci. 28 (2008) 5422–5432, <http://dx.doi.org/10.1523/JNEUROSCI.0955-08.2008>.
- [138] L.-H. Zeng, L. Xu, D.H. Gutmann, M. Wong, Rapamycin prevents epilepsy in a mouse model of tuberous sclerosis complex, Ann. Neurol. 63 (2008) 444–453, <http://dx.doi.org/10.1002/ana.21331>.
- [139] D.A. Krueger, A.A. Wilfong, K. Holland-Bouley, A.E. Anderson, K. Agricola, C. Tudor, et al., Everolimus treatment of refractory epilepsy in tuberous sclerosis complex, Ann. Neurol. 74 (2013) 679–687, <http://dx.doi.org/10.1002/ana.23960>.
- [140] J.A. French, J.A. Lawson, Z. Yapici, H. Ikeda, T. Polster, R. Nabbout, et al., Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study, Lancet 388 (2016) 2153–2163, [http://dx.doi.org/10.1016/S0140-6736\(16\)31419-2](http://dx.doi.org/10.1016/S0140-6736(16)31419-2).
- [141] S. Samuelli, K. Abraham, A. Dressler, G. Gröppel, A. Mühlebner-Fahrngruber, T. Scholl, et al., Efficacy and safety of Everolimus in children with TSC-associated epilepsy—pilot data from an open single-center prospective study, Orphanet J. Rare Dis. 11 (2016) 145, <http://dx.doi.org/10.1186/s13023-016-0530-z>.
- [142] L.M. Dibbens, B. de Vries, S. Donatello, S.E. Heron, B.L. Hodgson, S. Chintawar, et al., Mutations in DEPDC5 cause familial focal epilepsy with variable foci, Nat. Genet. 45 (2013) 546–551, <http://dx.doi.org/10.1038/ng.2599>.
- [143] S. Ishida, F. Picard, G. Rudolf, E. Noé, G. Achaz, P. Thomas, et al., Mutations of DEPDC5 cause autosomal dominant focal epilepsies, Nat. Genet. 45 (2013) 552–555, <http://dx.doi.org/10.1038/ng.2601>.
- [144] F. Picard, P. Makrythanasis, V. Navarro, S. Ishida, J. de Bellescize, D. Ville, et al., DEPDC5 mutations in families presenting as autosomal dominant nocturnal frontal lobe epilepsy, Neurology 82 (2014) 2101–2106, <http://dx.doi.org/10.1212/WNL.0000000000000488>.
- [145] D. Lal, E.M. Reinthaler, J. Schubert, H. Muhle, E. Riesch, G. Kluger, et al., DEPDC5 mutations in genetic focal epilepsies of childhood, Ann. Neurol. 75 (2014) 788–792, <http://dx.doi.org/10.1002/ana.24127>.
- [146] I.E. Scheffer, S.E. Heron, B.M. Regan, S. Mandelstam, D.E. Crompton, B.L. Hodgson, et al., Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations, Ann. Neurol. 75 (2014) 782–787, <http://dx.doi.org/10.1002/ana.24126>.
- [147] S. Baulac, S. Ishida, E. Marsan, C. Miquel, A. Biraben, D.K. Nguyen, et al., Familial focal epilepsy with focal cortical dysplasia due to DEPDC5 mutations, Ann. Neurol. 77 (2015) 675–683, <http://dx.doi.org/10.1002/ana.24368>.
- [148] C. Martin, C. Meloche, M.-F. Rioux, D.K. Nguyen, L. Carmant, E. Andermann, et al., A recurrent mutation in DEPDC5 predisposes to focal epilepsies in the French-Canadian population, Clin. Genet. 86 (2014) 570–574, <http://dx.doi.org/10.1111/cge.12311>.
- [149] L. Bar-Peled, L. Chantranupong, A.D. Cherniack, W.W. Chen, K.A. Ottina, B.C. Grabiner, et al., A Tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1, Science 340 (2013) 1100–1106, <http://dx.doi.org/10.1126/science.1232044>.
- [150] P.B. Crino, Evolving neurobiology of tuberous sclerosis complex, Acta Neuropathol. 125 (2013) 317–332, <http://dx.doi.org/10.1007/s00401-013-1085-x>.
- [151] J.H. Lee, M. Huynh, J.L. Silhavy, S. Kim, T. Dixon-Salazar, A. Heiberg, et al., De novo somatic mutations in components of the PI3K-AKT3-mTOR pathway cause hemimegalencephaly, Nat. Genet. 44 (2012) 941–945, <http://dx.doi.org/10.1038/ng.2329>.
- [152] E. Marsan, S. Ishida, A. Schramm, S. Weckhuysen, G. Muraca, S. Lecas, et al., Depdc5 knockout rat: a novel model of mTORopathy, Neurobiol. Dis. 89 (2016) 180–189, <http://dx.doi.org/10.1016/j.nbd.2016.02.010>.
- [153] A. Vezzani, Before epilepsy unfolds: finding the epileptogenesis switch, Nat. Med. 18 (2012) 1626–1627, <http://dx.doi.org/10.1038/nm.2982>.
- [154] A.S. Galanopoulou, J.A. Gorter, C. Cepeda, Finding a better drug for epilepsy: the mTOR pathway as an antiepileptogenic target, Epilepsia 53 (2012) 1119–1130, <http://dx.doi.org/10.1111/j.1528-1167.2012.03506.x>.
- [155] J.S. Lim, W.-I. Kim, H.-C. Kang, S.H. Kim, A.H. Park, E.K. Park, et al., Brain somatic mutations in MTOR cause focal cortical dysplasia type II leading to intractable epilepsy, Nat. Med. 21 (2015) 395–400, <http://dx.doi.org/10.1038/nm.3824>.
- [156] J.C. Sim, T. Scerri, M. Fanjul-Fernández, J.R. Riseley, G. Gillies, K. Pope, et al., Familial cortical dysplasia caused by mutation in the mammalian target of rapamycin regulator NPRL3, Ann. Neurol. 79 (2016) 132–137, <http://dx.doi.org/10.1002/ana.24502>.
- [157] G.-C. Korenke, M. Eggert, H. Thiele, P. Nürnberg, T. Sander, O.K. Steinlein, Nocturnal frontal lobe epilepsy caused by a mutation in the GATOR1 complex gene NPRL3, Epilepsia 57 (2016) e60–3, <http://dx.doi.org/10.1111/epi.13307>.
- [158] M.G. Ricos, B.L. Hodgson, T. Pippucci, A. Saidin, Y.S. Ong, S.E. Heron, et al., Mutations in the mammalian target of rapamycin pathway regulators NPRL2 and NPRL3 cause focal epilepsy, Ann. Neurol. 79 (2016) 120–131, <http://dx.doi.org/10.1002/ana.24547>.
- [159] S. Weckhuysen, E. Marsan, V. Lambrecq, C. Marchal, M. Morin-Breureau, I. An-Gourfinkel, et al., Involvement of GATOR complex genes in familial focal epilepsies and focal cortical dysplasia, Epilepsia 57 (2016) 994–1003, <http://dx.doi.org/10.1111/epi.13391>.
- [160] C. Liu, C. Lin, D.T. Whitaker, H. Bakeri, O.V. Bulgakov, P. Liu, et al., Prickle1 is expressed in distinct cell populations of the central nervous system and contributes to neuronal morphogenesis, Hum. Mol. Genet. 22 (2013) 2234–2246, <http://dx.doi.org/10.1093/hmg/ddt075>.
- [161] A.G. Bassuk, R.H. Wallace, A. Bühr, A.R. Buller, Z. Afawi, M. Shimojo, et al., A homozygous mutation in human PRICKLE1 causes an autosomal-recessive progressive myoclonus epilepsy-ataxia syndrome, Am. J. Hum. Genet. 83 (2008) 572–581, <http://dx.doi.org/10.1016/j.ajhg.2008.10.003>.
- [162] S.N. Ehaideb, A. Iyengar, A. Ueda, G.J. Iacobucci, C. Cranston, A.G. Bassuk, et al., Prickle modulates microtubule polarity and axonal transport to ameliorate seizures in flies, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 11187–11192, <http://dx.doi.org/10.1073/pnas.1403357111>.
- [163] L. Paemka, V.B. Mahajan, S.N. Ehaideb, J.M. Skeie, M.C. Tan, S. Wu, et al., Seizures are regulated by ubiquitin-specific peptidase 9 X-linked (USP9X), a de-ubiquitinase, PLoS Genet. 11 (2015) e1005022, <http://dx.doi.org/10.1371/journal.pgen.1005022>.
- [164] H. Tao, J.R. Manak, L. Sowers, X. Mei, H. Kiyonari, T. Abe, et al., Mutations in prickle orthologs cause seizures in flies, mice, and humans, Am. J. Hum. Genet. 88 (2011) 138–149, <http://dx.doi.org/10.1016/j.ajhg.2010.12.012>.
- [165] W.-H. Chung, S.-I. Hung, H.-S. Hong, M.-S. Hsieh, L.-C. Yang, H.-C. Ho, et al., Medical genetics: a marker for Stevens-Johnson syndrome, Nature 428 (2004), <http://dx.doi.org/10.1038/428486a>, 486–486.
- [166] W.-H. Chung, S.-I. Hung, J.-Y. Yang, S.-C. Su, S.-P. Huang, C.-Y. Wei, et al., Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis, Nat. Med. 14 (2008) 1343–1350, <http://dx.doi.org/10.1038/nm.1884>.
- [167] P. Chen, J.-J. Lin, C.-S. Lu, C.-T. Ong, P.F. Hsieh, C.-C. Yang, et al., Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan, N. Engl. J. Med. 364 (2011) 1126–1133, <http://dx.doi.org/10.1056/NEJMoa1009717>.
- [168] P.B. Ferrell, H.L. McLeod, Carbamazepine, HLA-B*1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations, Pharmacogenomics 9 (2008) 1543–1546, <http://dx.doi.org/10.2217/14622416.9.10.1543>.
- [169] U. Amstutz, N.H. Shear, M.J. Rieder, S. Hwang, V. Fung, H. Nakamura, 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 55 (2014) 496–506, <http://dx.doi.org/10.1111/epi.12564>.
- [170] Y.-K. Cheung, S.-H. Cheng, E.J.M. Chan, S.V. Lo, M.H.L. Ng, P. Kwan, HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in

- Han Chinese, *Epilepsia* 54 (2013) 1307–1314, <http://dx.doi.org/10.1111/epi.12217>.
- [171] S.-I. Hung, W.-H. Chung, Z.-S. Liu, C.-H. Chen, M.-S. Hsieh, R.C.-Y. Hui, et al., Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese, *Pharmacogenomics* 11 (2010) 349–356, <http://dx.doi.org/10.2217/pgs.09.162>.
- [172] T. Ozeki, T. Mushiroda, A. Yowang, A. Takahashi, M. Kubo, Y. Shirakata, 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.* 20 (2011) 1034–1041, <http://dx.doi.org/10.1093/hmg/ddq537>.
- [173] M. McCormack, A. Alfirevic, S. Bourgeois, J.J. Farrell, D. Kasperavičiūtė, M. Carrington, et al., HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans, *N. Engl. J. Med.* 364 (2011) 1134–1143, <http://dx.doi.org/10.1056/NEJMoa1013297>.
- [174] C.O. Plumpton, V.L.M. Yip, A. Alfirevic, A.G. Marson, M. Pirmohamed, D.A. Hughes, Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy, *Epilepsia* 56 (2015) 556–563.
- [175] J.N. LaBuzetta, J.Z. Yao, D.L. Bourque, J. Zivin, Adult nonhepatic hyperammonemia: a case report and differential diagnosis, *Am. J. Med.* 123 (2010) 885–891, <http://dx.doi.org/10.1016/j.amjmed.2010.02.029>.
- [176] P.K. Janicki, D. Bezinover, M. Postula, R.S. Thompson, J. Acharya, V. Acharya, et al., Increased occurrence of valproic acid-induced hyperammonemia in carriers of T1405N polymorphism in carbamoyl phosphate synthetase 1 gene, *ISRN Neurol.* 2013 (2013), <http://dx.doi.org/10.1155/2013/261497>, 261497–4.
- [177] R.M. Nanau, M.G. Neuman, Adverse drug reactions induced by valproic acid, *Clin. Biochem.* 46 (2013) 1323–1338, <http://dx.doi.org/10.1016/j.clinbiochem.2013.06.012>.
- [178] S. Petta, F.S. Macaluso, M.R. Barcellona, C. Cammà, D. Cabibi, V. Di Marco, et al., Serum γ -glutamyl transferase levels, insulin resistance and liver fibrosis in patients with chronic liver diseases, *PLoS One* 7 (2012) e51165, <http://dx.doi.org/10.1371/journal.pone.0051165>.
- [179] N. Ogusu, J. Saruwatari, H. Nakashima, M. Noai, M. Nishimura, M. Deguchi, et al., Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between valproic acid exposure and elevation of γ -glutamyltransferase in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis, *PLoS One* 9 (2014) e111066, <http://dx.doi.org/10.1371/journal.pone.0111066>.
- [180] H. Li, X. Wang, Y. Zhou, G. Ni, Q. Su, Z. Chen, et al., Association of LEPR and ANKK1 gene polymorphisms with weight gain in epilepsy patients receiving valproic acid, *Int. J. Neuropsychopharmacol.* 18 (2015) pyv021, <http://dx.doi.org/10.1093/ijnp/pyv021>.
- [181] A.J. Sadeque, M.B. Fisher, K.R. Korzekwa, F.J. Gonzalez, A.E. Rettie, Human CYP2C9 and CYP2A6 mediate formation of the hepatotoxin 4-ene-valproic acid, *J. Pharmacol. Exp. Ther.* 283 (1997) 698–703.
- [182] T. Bł̄di, K. Tóth, A. Nagy, Z. Szever, Á. Kiss, M. Temesvári, et al., Clinical significance of CYP2C9-status guided valproic acid therapy in children, *Epilepsia* 56 (2015) 849–855, <http://dx.doi.org/10.1111/epi.13011>.