Genetic Biomarkers in Epilepsy

Yvonne G. Weber · Anne T. Nies · Matthias Schwab ·
Holger Lerche

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Abstract The identification of valid biomarkers for outcome prediction of diseases and improvement of drug response, as well as avoidance of side effects is an emerging field of interest in medicine. The concept of individualized therapy is becoming increasingly important in the treatment of patients with epilepsy, as predictive markers for disease prognosis and treatment outcome are still limited. Currently, the clinical decision process for selection of an antiepileptic drug (AED) is predominately based on the patient's epileptic syndrome and side effect profiles of the AEDs, but not on effectiveness data. Although standard dosages of AEDs are used, supplemented, in part, by therapeutic monitoring, the response of an individual patient to a specific AED is generally unpredictable, and the standard care of patients in antiepileptic treatment is more or less based on trial and error. Therefore, there is an urgent need for valid predictive biomarkers to guide patient-tailored individualized treatment strategies in epilepsy, a research area that is still in its infancy. This review focuses on genomic factors as part of an individual concept for AED therapy summarizing examples that influence the prognosis of the disease and the response to AEDs, including side effects.

Keywords HLA · Sodium channels · Side effect · Prognosis · Pharmaco-resistance · Pharmacologic-response

Introduction

A biomarker is an objectively measured indicator for a biological or pathogenic process, including the outcome of a disease or a pharmacological response to a medication and its side effects [1, 2]. Many commonly used tests in the clinical diagnosis of epilepsy can serve as biomarkers, such as electroencephalography (EEG) and cerebral magnetic resonance imaging, or other electrophysiological or imaging methods. The research on genetic variations as potential biomarkers is a relatively new field in epilepsy but of increasing interest, especially for the treatment of patients with antiepileptic drugs (AEDs). We have divided the article into three parts, genetic biomarkers 1) for prognosis of the epilepsy syndrome; 2) for the response to medication; and 3) for the risk for side effects for selected AEDs. Examples of clinically relevant biomarkers are summarized in Table 1.

Genetic Biomarkers for Prognosis

More than 300 genes related to human epilepsy are known to date. Different mutations in many of those genes are associated with a wide phenotypic spectrum not clearly indicating a benign or severe course. However, genotype–phenotype correlations do exist and can help to predict a patient's outcome. In the next subsection, we focus on genes and epilepsy syndromes, for which knowledge is available that genetic variants may influence AED treatment.

Good Prognosis

It is evident that the clinical diagnosis of specific epilepsy syndromes, such as childhood absence epilepsy or Rolandic

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Y. G. Weber (✉) · H. Lerche (✉)
Department of Neurology and Epileptology, Hertie Institute for
Clinical Brain Research, University of Tübingen, Tübingen,
Germany
e-mail: yvonne.weber@uni-tuebingen.de
e-mail: holger.lerche@uni-tuebingen.de

A. T. Nies · M. Schwab
Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology,
Stuttgart, Germany

M. Schwab
Department of Clinical Pharmacology, University Hospital,
Tübingen, Germany

Table 1 Selected genetic biomarkers in epilepsy

Biomarker	Effect	Remarks
<i>KCNQ2/3</i> (K ⁺ channel gene)	Mainly good prognosis	BFNS, cave: bad prognosis in case of EE
<i>SCN2A</i> (Na ⁺ channel gene)	Mainly good prognosis	BFNIS, cave: bad prognosis with loss-of-function mutations and EE
<i>PRRT2</i> (gene encoding for presynaptic protein)	Good prognosis	BFIS and PKD
<i>SCN1A</i> (Na ⁺ channel gene)	Bad prognosis in case of truncation mutations Avoid Na ⁺ channel blockers	SMEI
<i>SLC2A1</i> (glucose transporter type 1 gene)	Broad pharmacoresistance to AEDs Good response to ketogenic diet	Glut1-associated syndromes
HLA-B*1502 HLA-B*1511	Stevens–Johnson syndrome/toxic epidermal necrolysis	Elevated risk in the Asian population upon CBZ and PHT therapy
HLA-A*3101	Hypersensitivity syndrome	Elevated risk in the European population upon CBZ therapy
CYP2C9, CYP2C19	Dose-related side effects	Impaired AED metabolism of PHT, PB

PRRT2 = proline-rich transmembrane protein gene 2; HLA = human leukocyte antigen; CYP = cytochrome P450; AED = antiepileptic drug; BFNS = benign familial neonatal seizures; EE = epileptic encephalopathy; BFNIS = benign familial neonatal–infantile seizures; BFIS = benign familial infantile seizures; PKD = paroxysmal kinesigenic dyskinesia; SMEI = severe myoclonic epilepsy of infancy; Glut1 = glucose transporter type 1; CBZ = carbamazepine; PHT = phenytoin; PB = phenobarbital

epilepsy, do not only include the seizure type, the typical age of onset, and EEG characteristics, but also knowledge of a frequently positive outcome. Genetic markers—if available—may improve the prediction of good prognosis in those syndromes and, importantly, render the diagnosis more certain in an early stage of the disease. One such example is outlined here, the benign familial epilepsy syndromes of neonates and infants [benign familial neonatal seizures (BFNS)/benign familial neonatal–infantile (BFNIS)/benign familial infantile seizures (BFIS)]. These syndromes are characterized by clusters of seizures in the first days (BFNS), weeks (BFNIS), or months (BFIS) of life, mostly disappearing spontaneously after weeks to months. The psychomotor development is normal in the majority of cases, but more recent studies have revealed cases with severe epileptic encephalopathy. Seizures have a partial onset often with hemitonic or hemiclonic symptoms, or with apnoeic spells, or can clinically appear as generalized. Interictal EEGs are often normal. The rare ictal EEGs recorded showed focal and generalized discharges. The risk of recurring seizures later in life is about 15 % (for a review see [3]).

The inheritance of BFNS is autosomal dominant, with a penetrance of 85 %. Mutations in the potassium channel genes *KCNQ2* and *KCNQ3* have been identified to cause BFNS [4–7]. The protein products—the voltage-gated channels K_v7.2 and K_v7.3—give rise to a slowly activating potassium current (so-called “M-current”), which regulates the firing rate of a neuron via tuning the membrane potential in the subthreshold range of an action potential [8]. The pathomechanism is a loss of function with haploinsufficiency [7] leading to a subthreshold membrane depolarization and increased neuronal firing. The identification of a mutation in *KCNQ2* or *KCNQ3* is associated with a positive prognosis and mostly seizure freedom in adulthood. Therefore,

an early reduction and stop of medication, for example at 6 months of age, is feasible. However, an increasing number of cases with mental retardation (“epileptic encephalopathy”) has been described [9–11], rendering the prognosis more difficult, as the mutations are not in different locations compared with those causing a benign course. Therefore, the mutations in the above-mentioned potassium channels cannot serve in all cases as a biomarker for a good prognosis. But electrophysiological analysis of the mutations in the severe forms revealed a dominant-negative effect in 5 of 7 studied mutations, which also affects the function of the wild-type allele, thereby explaining a much more severe course of the disease [12].

Dominant point mutations in the *SCN2A* gene encoding the alpha-subunit of the voltage-gated sodium channel Na_v1.2 are found in BFNIS [13]. Functional investigations have revealed a gain-of-function predicting an increased neuronal excitability [14, 15]. Patients with BFNIS have a good prognosis, and medication can be stopped early. However, there are very few patients described so far with more severe epilepsy [16], and some with epileptic encephalopathy [17]. In those, nonsense or missense mutations in the voltage sensor are often found, whereas BFNIS-associated mutations have never been described to be nonsense or with severe biophysical defects. Thus, in those cases, early detection of missense mutations in *SCN2A* usually predicts a good outcome, whereas nonsense mutations predict a bad outcome.

BFIS has the latest onset in this group of diseases and can be associated with paroxysmal kinesigenic dyskinesia. Recently, missense mutations in the gene *PRRT2* (proline-rich transmembrane protein 2) were described for both paroxysmal kinesigenic dyskinesia and BFIS, and the combination of both called infantile convulsions and choreoathetosis (ICCA)

[18–22]. The resulting protein might be functionally relevant in the vesicle synaptic metabolism of neurons as it interacts with SNAP25, which is a member of the SNARE complex responsible for the vesicle exocytosis into the synaptic cleft [18]. BFIS is always associated with a good prognosis, and *PRRT2* mutations were not found in 220 patients with epileptic encephalopathy [23]. However, BFIS cannot be distinguished by clinical criteria only from BFNIS, which might have a more severe prognosis. The identification of a mutation in *PRRT2* indicates a good prognosis with normal psychomotor development and mostly seizure freedom without medication in the long term. One family with a homozygous *PRRT2* mutation has been described to present with an epileptic encephalopathy [24] and in one patient with an intellectual disability [25].

Hence, genetics can help to predict outcome in the benign familial epilepsies of childhood. Particularly in sporadic cases with *de novo* mutations that lack a family history, the identified mutation can be used to predict prognosis early. There is also a perspective for the prediction of treatment response according to specific genotypes in these syndromes, which is outlined below.

Bad Prognosis

Idiopathic/genetic epilepsies with an unfavorable outcome concerning response to treatment and psychomotor development are commonly summarized as so-called “epileptic encephalopathies” (EE). The term EE comprises a variety of syndromes, including a severe and largely pharmacoresistant epilepsy, cognitive impairment and additional features, such as ataxia, which usually start after a normal birth and regular postnatal development. Each type of EE is individually rare, but together this group accounts for a significant proportion of childhood epilepsies. Clinically important examples of well-defined EEs are nonlesional infantile spasms, Ohtahara syndrome, severe myoclonic epilepsy of infancy (SMEI; also known as Dravet syndrome), epilepsy with electrical status epilepticus in sleep, and Lennox–Gastaut and Rett syndromes. The phenotypic variety is large, and not all EEs can be attributed to a specific entity [26, 27].

As an example with clinical consequences, SMEI will be described here in more detail. It is characterized by hemiclonic or generalized clonic, or tonic–clonic seizures in the first year of life that are often prolonged and associated with fever. During the course of the disease, patients develop afebrile generalized myoclonic, absence, or tonic–clonic seizures, but also simple and complex partial seizures occur. Cognitive deterioration appears in early childhood. In SMEI patients, mutations were found mainly in the sodium channel subunit gene *SCN1A* coding for Nav1.1 [28]. *SCN1A* is the gene with the most frequent mutations in epilepsy published to date, comprising a large spectrum of epilepsy phenotypes (<http://www.molgen.vib-ua.be/scn1amutations/>) [29]. At the benign end of the spectrum,

patients with generalized epilepsy with febrile seizures plus (GEFS+) and even simple familial febrile seizures have been described. GEFS+ represents a childhood-onset autosomal-dominant syndrome comprising febrile seizures and a variety of phenotypes, with afebrile seizure occurring often heterogeneously within the same pedigree. Most of the patients respond well to treatment and show a normal psychomotor development. Whereas point mutations in *SCN1A* are found in GEFS+ families, many of the SMEI patients carry *de novo* nonsense mutations predicting truncated proteins without function [30]. SMEI is resistant to pharmacotherapy in most cases, but stiripentol seems to have a significant positive effect [31]. The sodium channel blocker lamotrigine—the only drug of this class used in patients with idiopathic generalized epilepsies—can deteriorate the epilepsy in SMEI patients [32], supporting the pathogenic mechanism of a loss-of-function sodium channel disorder from a clinical point of view. Functional studies of *SCN1A* mutations in heterologous expression systems or mouse models revealed 1) predominantly loss-of-function mechanisms; 2) expression in inhibitory gamma aminobutyric acid-ergic interneurons and not in excitatory glutamatergic neurons; and 3) reduced firing exclusively in interneurons [33].

Concerning clinical management and prognosis, truncating or other deleterious mutations in *SCN1A* (that are detected, e.g., after the first or second prolonged febrile seizure, or later during the course of SMEI) serve as biomarkers to predict an unfavorable prognosis and a bad response to Na⁺ channel blockers. In addition, they help to identify the cause of the disease, thus avoid further costly and laborious diagnostics, and enable genetic counselling. In contrast, *SCN1A* point mutations in combination with a benign clinical course without signs of SMEI predict a favorable outcome.

Genetic Biomarkers for Pharmacoresponse

The availability of biomarkers would enable a concept of “personalized or individualized” medicine in the treatment of epilepsy. The vision is that the genetic constellation can predict the specific AED and potentially also the optimal dosage for one individual. To date, more than 30 AEDs are on the market. Comparative trials have revealed mostly none or small, but sometimes significant, differences between distinct AEDs for focal and generalized epilepsies [34–36], which influenced the recommendations in guidelines. However, the individual response of a patient to a specific drug cannot be predicted, and the usual way to select the right AED for the right patient is based 1) on the side effect profile, but mainly 2) on trial and error (<http://www.ilae.org/Visitors/Centre/Guidelines.cfm> and [37]). However, the prediction of AED efficacy is particularly important for approximately 30 % of pharmacoresistant patients who do not respond to the first or second AED [38]. It has been shown that about

15 % of pharmacoresistant patients become seizure-free after responding to the third, fourth, or later AED that is tried in the course of systematic treatment. This observation was independent of the AED used [39, 40]. Thus, there are clearly late responders to specific AEDs, as has been also shown in phase III trials designed to license new AEDs. A small percentage of patients always reach seizure freedom in such trials, although the observation time in these studies is usually limited to 3 months. To predict such late responses beforehand, genetic markers would avoid long periods of trial and error until the right drug is found. In addition, the individual dosage of an AED has to be tested in each patient, guided by the efficacy in controlling seizures and by side effects. The ability to predict the approximate dosage needed for each patient would also change our current clinical practice tremendously. The objective of a current European collaborative research project (EpiPGX: www.epipgx.eu) is to identify genetic markers for the efficacy and side effects of commonly used AEDs.

The response to an AED is influenced by many different parameters such as 1) the pathophysiology of the epilepsy itself (see above and next subsection); 2) the interaction of an AED with it(s) target(s) (pharmacodynamics effects); and 3) by the pharmacokinetics of the AED, involving mechanisms of absorption, distribution, metabolism, and elimination (ADME; Figs 1–2). In the following subsections we will describe the key features of these processes, including examples of genetic markers that can influence them.

Role of Pathophysiology of Epilepsy for Pharmacoresponse

We have already introduced some primary genetic epilepsy syndromes and will now discuss in more detail the impact of specific genetic variants on pharmacoresponse and their potential role as novel drug targets. In the case of *KCNQ2* mutations causing epileptic encephalopathy [11], a specific therapeutic approach is possibly feasible by enhancing the remaining activity of $K_{V7.2}$ channels with the recently labeled drug retigabine, which specifically acts on $K_{V7.2}$ channels [41, 42]. Pharmacoresistance in these patients may be overcome by the use of retigabine if other drugs fail. Furthermore, electrophysiological studies could predict response to retigabine for individual mutations, as specific mutations rarely reduce the sensitivity of $K_{V7.2}$ channels to retigabine [12]. In the case of severe *SCN2A* mutations with a loss of function [17], sodium channel blockers (similar to SMEI) should probably be avoided, whereas they should be beneficial in benign cases with gain-of-function mutations [14, 15]. These theoretical considerations need to be confirmed by clinical data, but indicate the importance of genetic information and its potential for innovative individualized drug therapy in epilepsy.

Another example indicating pharmacoresistance to AEDs is mutations in *SLC2A1* encoding the glucose transporter type 1 (Glut1). Glut1 delivers glucose to the brain across the blood–

brain barrier (BBB). The Glut1 syndromes comprise a variety of clinical features ranging from the most severe classical Glut1 deficiency syndrome, including pharmacoresistant epilepsy, mental retardation, microcephaly, and ataxia [43], to more benign courses in paroxysmal exertion-induced dyskinesia [44, 45], early-onset absence epilepsy [46], and also classical idiopathic/genetic generalized epilepsy [47, 48]. The functionally examined *SCL2A1* mutations lead to a relevant reduction of glucose uptake. All Glut1-associated syndromes are pharmacoresistant to standard AEDs, except for some mild cases [47]. They respond very well to a ketogenic diet, which bypasses the defective glucose metabolism by providing ketones as alternative energy carriers for the brain. Therefore, Glut1 syndromes are nice examples in which knowledge of the genotype is helpful in the management of patients in daily clinical practice.

Many of the commonly used AEDs are sodium channel blockers, such as phenytoin (PHT), carbamazepine (CBZ)/oxcarbazepine/eslicarbazepine and lamotrigine (LTG). One study suggested association of a polymorphism in *SCN1A* with the dosage of sodium channel blockers used in treated patients [49], but others could not confirm these results [50]. A more robust genetic association of polymorphisms in *SCN1A* with epilepsy has been reported in 2 recent genome-wide association studies [51, 52]; however, an association with pharmacoresponse has not been explored in these studies. Thus, the role of common polymorphisms in *SCN1A* or other genes encoding potential AED targets for pharmacoresponse needs to be elucidated in the future.

An interesting study using human tissue and a rodent model of temporal lobe epilepsy has suggested that variation in the physiological properties of voltage-gated sodium channels in brain slices affects the efficacy of carbamazepine [53]. More recently, the same group reported that a change of the beta subunit composition of the neuronal sodium channel complex might explain those findings [54]. However, here a possible link to a genetic polymorphism is also unclear.

Role of Variation in ADME Genes for Pharmacoresponse

Genetic, non-genetic, and epigenetic factors involved in ADME processes are potential determinants of a drug's pharmacokinetic property thereby contributing to the interindividual variability of drug response and/or side effects [55] (Fig. 1). Genetic polymorphisms in drug-metabolizing enzymes leading to distinct phenotypes are very well described, and evidence for their clinical significance with respect to side effects, drug efficacy, and dose requirements is rapidly growing [56]. While it was traditionally thought that drugs enter cells by passive diffusion it is now widely acknowledged that transporters (proteins integral to the plasma membrane facilitating the movement of compounds in and out of cells) are major determinants of drug absorption and elimination, as well as entry into the target organ (Fig. 2) [57–60]. The

Fig. 1 The efficacy of an antiepileptic drug (AED) can be influenced at many different sites involving drug absorption (**A**) in the gastrointestinal tract, distribution (**D**), and transport across the blood–brain barrier, drug action at a specific target within the brain, and hepatic and renal

metabolism/elimination (**ME**). Genetic variation, as well nongenetic factors and epigenetics, may affect expression and function of absorption, distribution, metabolism, and elimination (ADME) genes contributing to clinical outcome of AED therapy

potential role of drug transporters in resistance to antiepileptic drug therapy is currently being intensely discussed [61].

Drug absorption in the gastrointestinal tract results from the combined action of uptake and efflux transporters in the luminal membrane of the enterocytes. Among the different drug efflux transporters expressed in the enterocytes, MDR1 [P-glycoprotein (Pgp)], which is encoded by the *ABCB1* gene, is the best characterized. Several studies have associated AED plasma levels with 3 common and closely linked *ABCB1* polymorphisms (1236C > T, 2677G > T/A, and 3435C > T) [62, 63]. The variant 3435C > T has been proposed to be associated with lower levels of PHT [64], variants 3435C > T and 2677G > T/A with lower levels of CBZ [65], and the variant 1236C > T with lower levels of LTG [66]. The clinical relevance, however, is still controversial as some studies have shown a positive and some a negative association between *ABCB1* variants and response to AEDs [62].

Role of Drug Distribution for Pharmacoresponse

Antiepileptic drug therapy is efficiently restricted by the entry of AEDs into the brain as the target organ [67]. Therefore, membrane transporters at different brain barriers [BBB, blood–cerebrospinal fluid (CSF) barrier, CSF–brain barrier] are of major importance. It has been proposed that over-expression of efflux transporters at the BBB may be mechanistically responsible for pharmacoresistance of AED therapy. A recent review summarizes data on the cerebral expression of membrane drug

transporters, such as Pgp and multidrug resistance-associated proteins, and others in the epileptogenic brain, indicating that transporters in epileptogenic tissue are not only expressed in endothelial cells at the BBB, but also in brain parenchymal cells, such as astrocytes, microglia, and neurons [68]. Although most of the AEDs seem to be weak substrates of Pgp [62], animal experiments using *Mdr1a/1b*(-/-) and *Mdr1a/1b*(-/-)/*Bcrp*(-/-) mice showed that brain-to-plasma concentration ratios for several AEDs (e.g., phenobarbital, clobazam, zonisamide, gabapentin, tiagabine, levetiracetam, and topiramate) are significantly altered [69]. More than 10 years ago, increased expression of Pgp was associated with pharmacoresistant epilepsy in patients [70], as well as in animal models [71]. Moreover, the *ABCB1* variant 3435C > T has been proposed to influence brain penetration of phenobarbital. Epilepsy patients with the CC genotype had lower levels of phenobarbital in the CSF and exhibited higher seizure activity [72]. The first study, in 2003, suggested that the 3435C > T polymorphism may explain resistance to AED therapy in epilepsy [73], but several other association studies, as well as meta-analyses, have clearly demonstrated that the impact of *ABCB1* genetics on the pharmacoresistance of AEDs is inconsistent [62, 74, 75]. However, the concept that Pgp expression and function may be directly associated with pharmacoresistant temporal lobe epilepsy in patients has been very recently corroborated by a highly attractive approach investigating Pgp activity in patients with epilepsy using positron emission tomography technology [76]. Here, reduced focal (R)-[¹¹C]verapamil uptake was detected in

Fig. 2 Membrane drug transporters expressed at different tissues together with drug-metabolizing enzymes influence drug absorption, distribution, metabolism, and elimination (ADME) properties of a specific drug. MDR1 = multidrug resistance 1 protein; MRP = multidrug resistance-associated protein; BCRP = breast cancer resistant protein; OATP = organic anion transporter protein; PEPT1 = intestinal peptide cotransporter; OCT = organischer Kationentransporter

pharmacoresistant compared with seizure-free patients with temporal lobe epilepsy, and attenuated increases of (R)-[^{11}C]verapamil uptake after administration of the Pgp inhibition tariquidar in pharmacoresistant patients compared with healthy controls.

The metabolism and elimination of drugs depend on various proteins predominantly expressed in human liver and/or kidney (Fig. 1). Most of the AEDs are metabolized hepatically, and several phase 1 and 2 drug-metabolizing enzymes are involved. Membrane transporters are, again, important determinants for hepatic and renal elimination (Fig. 2). Genetic variability of drug-metabolizing enzymes has been the subject of research for more than 30 years. In particular, cytochrome P450 (CYPs) enzymes are of interest as several genetic variants in CYP isozymes have been identified in the past (<http://www.cypalleles.ki.se/>), substantially altering enzyme expression and function with clinical consequences (for a review see [56]). Regarding AEDs, only a few examples are known for which genetic variation of drug-metabolizing enzymes may be relevant. PHT is predominantly metabolized by CYP2C9 and, to a lesser extent, by CYP2C19. Loss-of-function polymorphisms in both of these liver enzymes result in impaired PHT metabolism and, consequently, to elevated plasma levels of PHT. Poor metabolizers who are carrying homozygous loss-of-function

variants are particularly at risk for the development of side effects as PHT is a drug with a narrow therapeutic window [77]. In this context, a very recent report indicates that PHT-induced cerebellar atrophy in patients with epilepsy may be linked to genetic variation of CYP2C9 [78]. Notably, recommendations on whether PHT dose adjustment should be performed in patients who are variant carriers for CYP2C9 and/or CYP2C19 are conflicting [62, 79]. This may be explained by several factors. First, several enzymes (CYP2C9, CYP2C19) and transporter proteins (e.g., ABCB1) are involved in PHT disposition; therefore, alteration of PHT plasma levels does not depend only on variation of one candidate gene. Second, other pharmacological processes like protein induction or inhibition may influence the expression and function of enzymes and transporters, as recently considered for AEDs [80]. Third, other mechanisms like epigenetics may influence ADME targets such as miRNAs and CYP expression [81], or DNA methylation and transporter expression [82].

Regarding other AEDs, valid data are missing on whether genetic variation of drug-metabolizing enzymes and/or transporters significantly contribute to side effects or/and treatment outcome. For instance, it has been suggested that tubular secretion of gabapentin, which is predominantly eliminated via the renal route, is altered by a genetic variant (L503F) in

the organic cation transporter novel subfamily 1, resulting in a reduced renal clearance [83].

In addition to genetic variation in ADME genes, non-genetic factors may also contribute to side effects and/or treatment outcome. Promising studies exist in which multivariate models, including genetics, as well as age, gender, and body weight, were used for predicting PHT and CBZ dosing in epilepsy patients [84, 85].

Genetic Biomarkers for Hypersensitivity Reactions of AEDs

AED therapy is the most important, and always first, treatment for epilepsy patients. As epilepsy is a chronic disease, many patients receive life-long antiepileptic medication. AED therapy is very effective as 60–70 % of patients become seizure-free with the first or second AED tried [86, 87], but side effects are common. More than a third of patients develop specific side effects on AEDs, but we are not able to predict who will suffer from which side effect in which dosage. Most AEDs have common side effects, such as dizziness or somnolence. Prominent examples of specific side effects of commonly used AEDs are weight gain, tremor, and alopecia for valproate; rash for CBZ or LTG; hyponatremia for oxcarbazepine or eslicarbazepine; irritability for levetiracetam; and weight loss, as well as cognitive impairment including speech problems, for topiramate [88].

Recently, genetic biomarkers for side effects of AEDs have been approved by the US Food and Drug Administration. Severe allergic skin reactions, such as Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can appear upon treatment with CBZ. SJS is characterized by initial fever and fatigue combined with ulcers on mucous membranes such as mouth and lips. TEN is the worst form of SJS, with a mortality of up to 40 %. The human leucocyte antigen (HLA) allele HLA-B*1502 is strongly associated with severe allergic skin reactions upon CBZ therapy in the Chinese population [89]. The US Food and Drug Administration has therefore recommended obtaining HLA status before treatment with CBZ in Asian patients since 2008. HLA-B*1502 does not seem to be a predictive marker for CBZ-induced skin reactions in the Korean and Japanese populations, while HLA-B*1511 is a predictor in these Asian subgroups [90, 91]. In a prospective study with more than 4000 patients considered for treatment with CBZ in Taiwan it was shown that genetic testing completely prevents SJS and TEN when all patients carrying the HLA-B*1502 allele (7.7 %) are treated with other AEDs [92]. The association of HLA-B*1502 was also found for PHT [93], but not for LTG [94]. In the European population, an association of HLA-A*3101 was found for all hypersensitivity syndromes with CBZ treatment [95], but not with LTG or PHT [96]. The HLA-A*3101 allele was also identified in the

Japanese population as risk factor for CBZ-induced cutaneous adverse drug reactions [97].

In daily practice, the HLA-B*1502 allele should be tested for before the start of CBZ in patients of Asian ancestry. In the European population, severe allergic skin reactions are less common, and a prospective study has not been performed yet. As CBZ has other disadvantages, in particular enzyme induction, CBZ is no longer considered as first-line therapy in the treatment of epilepsy, at least in Germany, according the guidelines of the German Society for Neurology (<http://www.dgn.org/leitlinien.html>).

Conclusion

Genetic biomarkers and pharmacogenomics constitute an emerging field with a huge potential to influence our decisions for treatment of epilepsy in the future. *SCN1A*-related epilepsies and Glut1-associated syndromes provide nice examples of how genetics can influence both clinical management and antiepileptic therapy. Further examples might be *KCNQ2*- and *SCN2A*-related epilepsies. Concerning side effects, severe cutaneous reactions can be avoided by genetic testing in South Asian populations. Further development of novel genetic techniques and their application for clinical management will certainly contribute to the development of more relevant genetic biomarkers and enable their clinical use. The relationship between a patient's phenotype (e.g., drug response), which may change over time, and genotype needs to be more deeply considered. A more comprehensive integration of nongenetic factors, such as environmental and clinical covariates, may provide important additional phenotypic information to increase the precision of a therapeutic decision [55, 98]. Large multicentre studies, which have been already initiated, will be necessary to reach the goal of a broader understanding of pharmacogenomic mechanisms in the epilepsies.

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References

1. Larson H, Chan E, Sudarsanam S, Johnson DE. Biomarkers. *Methods Mol Biol* 2013;930:253–273.

2. Engel J Jr, Pitkänen A, Loeb JA, et al. Epilepsy biomarkers. *Epilepsia* 2013;54:61-69.
3. Weber YG, Lerche H. Genetic mechanism in epilepsy. *Develop Med Child Neurol* 2008;50:648-654.
4. Biervert C, Schroeder BC, Kubisch C, et al. A potassium channel mutation in neonatal human epilepsy. *Science* 1998;279:403-406.
5. Charlier C, Singh NA, Ryan SG, et al. A pore mutation in a novel KQT-like potassium channel gene in an idiopathic epilepsy family. *Nat Genet* 1998;18:53-55.
6. Singh NA, Charlier C, Stauffer D, et al. A novel potassium channel gene, *KCNQ2*, is mutated in an inherited epilepsy of newborns. *Nat Genet* 1998;18:25-29.
7. Maljevic S, Wuttke TV, Seeböhm G, Lerche H. KV7 channelopathies. *Pflugers Arch* 2010;460:277-288.
8. Delmas P, Brown DA. Pathways modulating neural *KCNQ/M* (Kv7) potassium channels. *Nat Rev Neurosci* 2005;6:850-862.
9. Borgatti R, Zucca C, Cavallini A, et al. A novel mutation in *KCNQ2* associated with BFNC, drug resistant epilepsy, and mental retardation. *Neurol* 2004;63:57-65.
10. Steinlein OK, Conrad C, Weidner B. Benign familial neonatal convulsions: always benign? *Epilepsy Res* 2007;73:245-249.
11. Weckhuysen S, Mandelstam S, Suls A, et al. *KCNQ2* encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. *Ann Neurol* 2012;71:15-25.
12. Orhan G, Bock M, Schepers D, et al. Dominant-negative effects of *KCNQ2* mutations are associated with epileptic encephalopathy. *Ann Neurol* 2013 Dec 7 [Epub ahead of print].
13. Heron SE, Crossland KM, Andermann E, et al. Sodium-channel defects in benign familial neonatal-infantile seizures. *Lancet* 2002;360:851-852.
14. Scalmani P, Rusconi R, Armatura E, et al. Effects in neocortical neurons of mutations of the Na(v)1.2 Na⁺ channel causing benign familial neonatal-infantile seizures. *J Neurosci* 2006;26:10100-10109.
15. Liao Y, Deprez L, Maljevic S, et al. Molecular correlates of age-dependent seizures in an inherited neonatal-infantile epilepsy. *Brain* 2010;133:1043-1014.
16. Liao Y, Anttonen AK, Liukkonen E, et al. *SCN2A* mutation associated with neonatal epilepsy, late-onset episodic ataxia, myoclonus, and pain. *Neurology* 2010;75:14554-14558.
17. Ogiwara I, Ito K, Sawaishi Y, et al. De novo mutations of voltage-gated sodium channel α II gene *SCN2A* in intractable epilepsies. *Neurology* 2009;73:1046-1053.
18. Chen WJ, Lin Y, Xiong ZQ, et al. Exome sequencing identifies truncating mutations in *PRRT2* that cause paroxysmal kinesigenic dyskinesia. *Nat Genet* 2011;43:1252-1255.
19. Lee HY, Huang Y, Bruneau N, et al. Mutations in the novel protein *PRRT2* cause paroxysmal kinesigenic dyskinesia with infantile convulsions. *Cell Rep* 2012;26:2-12.
20. Heron SE, Grinton BE, Kivity S, et al. *PRRT2* mutations cause benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome. *Am J Hum Genet* 2012;90:152-160.
21. Schubert S, Paravidino R, Becker F, et al. *PRRT2* mutations are the major cause of benign familial infantile seizures (BFIS). *Hum Mutat* 2012;33:1439-1443.
22. Becker F, Schubert J, Striano P, et al. *PRRT2*-related disorders: Further PKD and ICCA cases and review of the literature. *J Neurol* 2013;260:1234-1244.
23. Heron SE, Ong YS, Yendle SC, et al. Mutations in *PRRT2* are not a common cause of infantile epileptic encephalopathies. *Epilepsia* 2013;54:e86-89.
24. Labate A, Tarantino P, Viri M, et al. Homozygous c.649dupC mutation in *PRRT2* worsens the BFIS/PKD phenotype with mental retardation, episodic ataxia, and absences. *Epilepsia* 2012;53:e196-199.
25. Najmabadi H, Hu H, Garshasbi M, et al. Deep sequencing reveals 50 novel genes for recessive cognitive disorders. *Nature* 2011;479:57-63.
26. Covanis A. Epileptic encephalopathies (including severe epilepsy syndromes). *Epilepsia* 2012;53(Suppl. 4):114-126.
27. von Spiczak S. Genetische Ursachen epileptischer Enzephalopathien. *Z Epileptol* 2011;24:108-113.
28. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene *SCN1A* cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 2001;68:1327-1332.
29. Harkin LA, McMahon JM, Iona X, et al. The spectrum of *SCN1A*-related infantile epileptic encephalopathies. *Brain* 2007;130: 843-852.
30. Gambardella A, Marini C. Clinical spectrum of *SCN1A* mutations. *Epilepsia* 2009;50(Suppl. 5):20-23.
31. Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 2000;356: 1638-1642.
32. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. *Epilepsia* 1998;39:508-512.
33. Lerche H, Shah M, Beck H, Noebels JL, Johnston D, Vincent A. Ion channels in genetic and acquired forms of epilepsy. *J Physiol* 2013;591:753-764.
34. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet* 2007;369:1012-1026.
35. Marson AG, Al-Kharusi AM, Alwaidh M, et al. The SANAD study of effectiveness carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled study. *Lancet* 2007;369: 1000-1015.
36. Glauser TA, Cnaan A, Shinnar S, et al. Childhood Absence Epilepsy Study Group. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. *N Engl J Med* 2010;362:790-799.
37. Klammer S, Singh A, Gil-Nagel A, et al. Current recommendations, guidelines, and expert views of practical anticonvulsant therapy. In: Lerche H, Potschka H (eds) *Therapeutic targets and perspectives in the pharmacological treatment of epilepsy*. Germany, UNI-MED Verlag AG, 2013, pp. 26-36.
38. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia* 2010;51:1069-1077.
39. Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. *Ann Neurol* 2007;62:382-389.
40. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol* 2007;62: 375-381.
41. Rundfeldt C, Netzer R. The novel anticonvulsant retigabine activates M-currents in Chinese hamster ovary-cells transfected with human *KCNQ2/3* subunits. *Neurosci Lett* 2000;282:73-76.
42. Wuttke TV, Seeböhm G, Bail S, Maljevic S, Lerche H. The new anticonvulsant retigabine favors voltage-dependent opening of the Kv7.2 (*KCNQ2*) channel by binding to its activation gate. *Mol Pharmacol* 2005;67:1009-1017.
43. Seidner G, Alvarez MG, Yeh JI, et al. *GLUT-1* deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. *Nat Genet* 1998;18:188-191.
44. Weber YG, Storch A, Wuttke TV, et al. *GLUT1* mutations are a cause of paroxysmal exercise-induced dyskinesias and induce hemolytic anemia by a cation leak. *J Clin Invest* 2008;118: 2157-2168.
45. Suls A, Dedeken P, Goffin K, et al. Paroxysmal exercise-induced dyskinesia and epilepsy is due to mutations in *SLC2A1*, encoding the glucose transporter *GLUT1*. *Brain* 2008;131:1831-1844.

46. Suls A, Mullen SA, Weber YG, et al. Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT1. *Ann Neurol* 2009;66:415-419.
47. Striano P, Weber YG, Toliaat MR, et al. GLUT1-mutations are a rare cause of familial idiopathic generalized epilepsy. *Neurology* 2012;78:557-562.
48. Arsov T, Mullen SA, Rogers S, et al. Glucose transporter 1 deficiency in the idiopathic generalized epilepsies. *Ann Neurol* 2012;72:807-815.
49. Tate SK, Depondt C, Sisodiya SM, et al. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proc Natl Acad Sci U S A* 2005;102:5507-5512.
50. Zimprich F, Stogmann E, Bonelli SB, et al. A functional polymorphism in the SCN1A gene is not associated with carbamazepine dosages in Austrian patients with epilepsy. *Epilepsia* 2008;49:1108-1109.
51. EPICURE Consortium; EMINet Consortium, Steffens M, et al. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. *Hum Mol Genet* 2012;21:5359-5372.
52. Kasperaviciute D, Catarino CB, Matarin M, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. *Brain* 2013;136:3140-3150.
53. Remy S, Gabriel S, Urban BW, et al. A novel mechanism underlying drug resistance in chronic epilepsy. *Ann Neurol* 2003;53:469-479.
54. Uebachs M, Opitz T, Royeck M, Dickhof G, Horstmann MT, Isom LL, Beck H. Efficacy loss of the anticonvulsant carbamazepine in mice lacking sodium channel beta subunits via paradoxical effects on persistent sodium currents. *J Neurosci* 2010;30:8489-8501.
55. Meyer UA, Zanger UM, Schwab M. Omics and drug response. *Annu Rev Pharmacol Toxicol* 2013;53:475-502.
56. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther* 2013;138:103-141.
57. Nies AT, Schwab M, Keppler D. Interplay of conjugating enzymes with OATP uptake transporters and ABCC/MRP efflux pumps in the elimination of drugs. *Expert Opin Drug Metab Toxicol* 2008;4:545-568.
58. Giacomini KM, Huang SM, Tweedie DJ, et al. Membrane transporters in drug development. *Nat Rev Drug Discov* 2010;9:215-236.
59. Kell DB, Dobson PD, Oliver SG. Pharmaceutical drug transport: the issues and the implications that it is essentially carrier-mediated only. *Drug Discov Today* 2011;16:704-714.
60. DeGorter MK, Xia CQ, Yang JJ, Kim RB. Drug transporters in drug efficacy and toxicity. *Annu Rev Pharmacol Toxicol* 2012;52:249-273.
61. Potschka H. Role of CNS efflux drug transporters in antiepileptic drug delivery: overcoming CNS efflux drug transport. *Adv Drug Deliv Rev* 2012;64:943-952.
62. Löscher W, Klotz U, Zimprich F, Schmidt D. The clinical impact of pharmacogenetics on the treatment of epilepsy. *Epilepsia* 2009;50:1-23.
63. Stepień KM, Tomaszewski M, Tomaszewska J, Czuczwar SJ. The multidrug transporter P-glycoprotein in pharmacoresistance to antiepileptic drugs. *Pharmacol Rep* 2012;64:1011-1019.
64. Ebid AH, Ahmed MM, Mohammed SA. Therapeutic drug monitoring and clinical outcomes in epileptic Egyptian patients: a gene polymorphism perspective study. *Ther Drug Monit* 2007;29:305-312.
65. Simon C, Stieger B, Kullak-Ublick GA, et al. Intestinal expression of cytochrome P450 enzymes and ABC transporters and carbamazepine and phenytoin disposition. *Acta Neurol Scand* 2007;115:232-242.
66. Lovrić M, Božina N, Hajnšek S, et al. Association between lamotrigine concentrations and ABCB1 polymorphisms in patients. *Ther Drug Monit* 2012;34:518-525.
67. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiol Dis* 2010;37:13-25.
68. Aronica E, Sisodiya SM, Gorter JA. Cerebral expression of drug transporters in epilepsy. *Adv Drug Deliv Rev* 2012;64:919-929.
69. Nakanishi H, Yonezawa A, Matsubara K, Yano I. Impact of P-glycoprotein and breast cancer resistance protein on the brain distribution of antiepileptic drugs in knockout mouse models. *Eur J Pharmacol* 2013;710:20-28.
70. Dombrowski SM, Desai SY, Marroni M, et al. Overexpression of multiple drug resistance genes in endothelial cells from patients with refractory epilepsy. *Epilepsia* 2001;42:1501-1506.
71. van Vliet E, Redeker S, Aronica E, et al. Expression of multidrug transporters MRP1, MRP2, and BCRP shortly after status epilepticus, during the latent period, and in chronic epileptic rats. *Epilepsia* 2005;46:1569-1580.
72. Basic S, Hajnšek S, Božina N, Filipčić I, Sporis D, Mislov D, Posavec A. The influence of C3435T polymorphism of ABCB1 gene on penetration of phenobarbital across the blood-brain barrier in patients with generalized epilepsy. *Seizure* 2008;17:524-530.
73. Siddiqui A, Kerb R, Weale ME, et al. Association of multidrug resistance in epilepsy with a polymorphism in the drug-transporter gene ABCB1. *N Engl J Med* 2003;348:1442-1448.
74. Bournissen FG, Moretti ME, Juurlink DN, Koren G, Walker M, Finkelstein Y. Polymorphism of the MDR1/ABCB1 C3435T drug-transporter and resistance to anticonvulsant drugs: a meta-analysis. *Epilepsia* 2009;50:898-903.
75. Haerian BS, Roslan H, Raymond AA, et al. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. *Seizure* 2010;19:339-346.
76. Feldmann M, Asselin MC, Liu J, et al. P-glycoprotein expression and function in patients with temporal lobe epilepsy: a case-control study. *Lancet Neurol* 2013;12:777-785.
77. Hung CC, Huang HC, Gao YH, et al. Effects of polymorphisms in six candidate genes on phenytoin maintenance therapy in Han Chinese patients. *Pharmacogenomics* 2012;13:1339-1349.
78. Twardowsky CA, Werneck LC, Scola RH, Borgio JG, De Paola L, Silvado C. The role of CYP2C9 polymorphisms in phenytoin-related cerebellar atrophy. *Seizure* 2013;22:194-197.
79. Kerb R, Aynacioglu AS, Brockmüller J, et al. The predictive value of MDR1, CYP2C9, and CYP2C19 polymorphisms for phenytoin plasma levels. *Pharmacogenomics* 2001;1:204-210.
80. Brodie MJ, Mintzer S, Pack AM, Gidal BE, Vecht CJ, Schmidt D. Enzyme induction with antiepileptic drugs: cause for concern? *Epilepsia* 2013;54:11-27.
81. Rieger JK, Klein K, Winter S, Zanger UM. Expression variability of absorption, distribution, metabolism, excretion-related microRNAs in human liver: influence of nongenetic factors and association with gene expression. *Drug Metab Dispos* 2013;41:1752-1762.
82. Schaeffeler E, Hellerbrand C, Nies AT, et al. DNA methylation is associated with downregulation of the organic cation transporter OCT1 (SLC22A1) in human hepatocellular carcinoma. *Genome Med* 2011;3:82.
83. Urban TJ, Brown C, Castro RA, et al. Effects of genetic variation in the novel organic cation transporter, OCTN1, on the renal clearance of gabapentin. *Clin Pharmacol Ther* 2008;83:416-421.
84. Chaudhry AS, Urban TJ, Lamba JK, et al. CYP2C9*1B promoter polymorphisms, in linkage with CYP2C19*2, affect phenytoin autoinduction of clearance and maintenance dose. *J Pharmacol Exp Ther* 2010;332:599-611.
85. Makmor-Bakry M, Sills GJ, Hitiris N, Butler E, Wilson EA, Brodie MJ. Genetic variants in microsomal epoxide hydrolase influence carbamazepine dosing. *Clin Neuropharmacol* 2009;32:205-212.
86. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? *Seizure* 2000;9:464-468.
87. Brodie MJ, Barry SJ, Bamagous GA, Norrie JD, Kwan P. Patterns of treatment response in newly diagnosed epilepsy. *Neurology* 2012;78:1548-1554.

88. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol* 2012;11:792-802.
89. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16:297-306.
90. Kim SH, Lee KW, Song WJ, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res* 2011;97:190-197.
91. Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 2010 ;51:2461-2465.
92. Chen P, Lin JJ, Lu CS, et al. Taiwan SJS Consortium, Carbamazepine-induced toxic effects and HLA-B*1502 screenin gin Taiwan, *N Engl J Med* 2011;346:1126-1133.
93. Cheung YK, Cheng SH, Chan EJ, Lo SV, Ng MH, Kwan P. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. *Epilepsia* 2013;54:1307-1314.
94. An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. *Epilepsy Res* 2010;92: 226-230.
95. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med* 2011;364:1134-1143.
96. McCormack M, Urban TJ, Shianna KV, et al. Genome-wide mapping for clinically relevant predictors of lamotrigine- and phenytoin-induced hypersensitivity reactions. *Pharmacogenomics* 2012;13: 399-405.
97. Ozeki T, Mushiroda T, Yowang A, 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* 2011;20:1034-1041.
98. Schwab M, Schaeffeler E. Pharmacogenomics: a key component of personalized therapy. *Genome Med* 2012;4:93.