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# Pharmacogenetics and the treatment of epilepsy: what do we know?

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## Abstract

Seizure control with antiepileptic drugs (AEDs) as well as susceptibility to adverse drug reactions varies among individuals with epilepsy. This interindividual variability is partly determined by genetic factors. However, genetic testing to predict the efficacy and toxicity of AEDs is limited and genetic variability is, as yet, largely unexplainable. Accordingly, genetic testing can only be advised in a very limited number of cases in clinical routine. Currently, by applying different methodologies, many trials have been undertaken to evaluate cost benefits of preventive pharmacogenetic analysis for patients. There is significant progress in sequencing technologies, and focus is on next-generation sequencing-based methods, like exome and genome sequencing. In this review, an overview of the current scientific knowledge considering the pharmacogenetics of AEDs is given.

Keywords: adverse drug reactions • antiepileptic drugs • drug metabolism • gene polymorphism • pharmacogenetics • pharmacoresistance

## Introduction

Seizure control with antiepileptic drugs (AEDs) as well as susceptibility to adverse drug reactions (ADRs) differs among individuals with epilepsy. Remission fails to occur in a third of epilepsy patients in spite of taking appropriate AEDs [1], and about a third of patients develop at least one ADR to AEDs [2]. This variability is believed to be in part due to genetic factors [3].

## The role of genetic variants in response to AEDs

Genes can affect drug response influencing pharmacokinetic parameters by causing variable activity of the systems responsible for the metabolism and transport of the drug (ADME genes – absorption, distribution, metabolism, excretion) as well as influencing pharmacodynamics through drug targets [4]. Advances in genomic testing have also enabled numerous epilepsy genes responsible for the majority of nonacquired epilepsies to be identified [5].

**Genetic influence on AED metabolism**

Drug metabolism may be under significant genetic influence, which can induce changes in the expression and activity of certain enzymes [4]. Among Phase I biotransformation enzymes, genetic polymorphisms of CYP450 enzymes, CYP2C9, CYP2C19 and CYP3A4/3A5, and in Phase II genetic polymorphisms of UDP-UGTs are of the greatest clinical relevance for AEDs [4,6]. Phenytoin is metabolized primarily by CYP2C9 and, to a minor extent, by CYP2C19. Loss of function variants in the alleles coding for both of these enzymes results in reduced phenytoin clearance, increased serum phenytoin concentrations and a higher risk of concentration-dependent neurotoxicity.More than 50 variant alleles have been identified in the *CYP2C9* gene, indicating its high polymorphism. The most important are **2* (3608C>T, rs1799853) and *3 (42614A>C, rs1057910) alleles. According to the gene-based dosing recommendations for phenytoin, individuals having two decreased function alleles (**2/*2, *3/*3, *2/*3*) of the *CYP2C9* should have 50% reduction of starting maintenance dose compared with active allele carriers (**1*) (Table 1) [7]. *CYP2C9*3* polymorphism was found to be associated with serious cutaneous ADRs (cADRs) induced by phenytoin [8].

Phenobarbital (PB) is metabolized through multiple pathways, but genetic influence seems to be related mostly to *CYP2C19* polymorphism. More than 25 variant alleles are known in the *CYP2C19* gene, of which the most studied are alleles with reduced activity, **2* (c.681G>A, rs4244285) and **3* (c.636G>A, rs4986893) alleles, as well as the **17* (c.-806C> T, rs12248560) allele, which is associated with enhanced enzyme activity. Studies have shown the body clearance of PB is reduced by 20% in patients with inactive alleles (*CYP2C19*2,*3*) compared with active allele (**1*) carriers [9]. In one study, the effect of *CYP2C19* variants on PB clearance was not detected, but total clearance was decreased by almost 50% in patients with *CYP2C9*1/*3* genotype as compared with *CYP2C9 *1/*1* carriers [10].

Zonisamide (ZNS) is eliminated by renal excretion of 2-sulfamoylacetyl-phenol-glucuronide (50%), native unchanged form (35%) and *N*-acetyl ZNS (15%). *In vitro* data showed the formation of 2-sulfamoylacetylphenol to be catalyzed mainly by CYP3A4 and to a lesser extent by CYP3A5 and CYP2C19 [11]. One study in a Japanese population with epilepsy showed that clearance of ZNS was lower in the CYP2C19 intermediate and poor metabolizers as compared with homozygous, extensive metabolizers (16 vs 30%) [12].

Brivaracetam is primarily metabolized by hydrolysis to an inactive metabolite, and to a minor extent by CYP2C19-dependent hydroxylation. Individuals who are CYP2C19 poor metabolizers could have greater exposure to standard doses of drug and increased risk of adverse effects. In humans with one or both mutated *CYP2C19* alleles, blood level of brivaracetam was increased by 22 and 42%, respectively [13].

Several studies have also shown the association between *CYP2C19* polymorphisms and serum concentration of pharmacologically active metabolite of clobazam (CLB), *N*-clobazam (N-CLB). Patients homozygous for mutated *CYP2C19* alleles had significantly higher N-CLB concentration/CLB dose ratios as compared with those with the wild-type genotype. According to one study, the difference was more than sixfold [14]. On population scale, the relevance of *CYP2C19* gene variability is different, since there is great interethnic variability in the proportion of poor and ultrarapid metabolizers of CYP2C19 [15]. It has been estimated that 2–5% of Caucasians and 20% of Asians are CYP2C19 poor metabolizers [16].

The major enzymes involved in lacosamide metabolism are CYP2C19, CYP2C9, CYP3A4, but there are still no clear associations of their polymorphisms with lacosamide pharmacokinetics, although the amount of lacosamide metabolite excreted into urine was reduced by about 70% in CY2C19 poor metabolizers compared with extensive metabolizers [17].

A subfamily of CYP3A enzymes is involved in the metabolism of 50% of all drugs used in clinical routine [18]. CYP3A4/3A5 share substrates and exhibit very high variability in activity, which is of particular relevance to drug substrates with narrow therapeutic range, including some AEDs. Although CYP3A4 has a great number of known polymorphisms, most of these are very rare and cannot reflect significant interindividual variability in the phenotypic effect *in vivo* [11,19]. Promoter variant *CYP3A4*1B* is according to some [20] but not all studies [21] associated with enhanced CYP3A4 expression, while *CYP3A4*22* variant predispose to reduced CYP3A4 protein expression levels [22]. In addition to genetic predisposition, CYP3A4 variability is strongly influenced by environmental factors such as food (e.g., grapefruit juice), smoking and other drugs. These factors contributed to 20% of its variability [23,24].

Carbamazepine (CBZ) is metabolized by several enzymes, including CYP3A4, CYP3A5, CYP2C8, EPHX1 and UGT2B7 [25]. *EPHX1* variants were found to affect CBZ pharmocokinetics and pharmacodynamics by causing functional changes of microsomal epoxide hydrolase. An *in vitro* study demonstrated CBZ metabolism is influenced by two *EPHX1* variants, c.337T>C and c.416A>G. Microsomal epoxide hydrolase activity was decreased in association with variant 416G allele, while it was increased in association with variant 337C allele when using CBZ-10,11-epoxide as substrate [26]. Two separate *in vivo* studies confirmed these results, demonstrating the carriers of the variant 337C allele to have higher CBZ doses or lower CBZ concentration-dose ratios as compared with noncarriers [27]. Another study showed the patients with the variant c.416A>G genotypes to have higher adjusted CBZ concentrations than those with the wild-type [26,27]. *CYP3A5* expressers are reported to have a significantly lower dose-adjusted CBZ concentration [28].

Valproic acid (VPA) ismetabolized by glucuronidation in the liver (50%), β-oxidation in themitochondria (40%) and CYP-mediated oxidation (CYP2C9, 2C19, 2B6, 2D6), considered a minor route, approximately 10% [29].

Numerous studies investigated the influence of *UGT2B7* variants on VPA plasma concentrations. A recent metaanalysis showed the *UGT2B7* 211G>T and 161C>T polymorphisms to influence VPA pharmacokinetics [30].

VPA-induced liver damage was found to be associated with VPA biotransformation to its hepatotoxic metabolite via CYP2C9 [31].

Lamotrigine is eliminated almost entirely by glucuronidation, and the main metabolic enzyme is UGT1A4. *UGT1A4*3* variant may affect the bioavailability and efficacy of lamotrigine [32]. Association has also been reported between *UGT2B7* c.802T>C variant and maintenance doses of oxcarbazepine (OXC), which may be useful for OXC therapy-personalization [33].

**Genetic predictive factors for pharmacoresistance & drug response**

Predictive markers of resistance were sought among the genes encoding drug transporters and target molecules of AED activity, such as sodium and potassium channels.

Transport proteins are important in drug transport through various biological membranes, therefore gene polymorphisms may affect the regulation of absorption, distribution and excretion of many drugs [34]. One of the best described transporters is the efflux transporter P-gp encoded by the *MDR1/ABCB1* gene. In the brain, P-gp is expressed in astrocytes, endothelial cells and neurons [35]. Overexpression of P-gp in epileptic tissue was found associated with pharmacoresistance to AEDs in some studies [36]. While some studies found correlation of *ABCB1* 3435CC genotype with resistance to AED [37], many other did not confirm it [38,39], nor for other *ABCB1* variants (1236C >T, 2677G >T) [40]. Results of studies investigating the correlation of *ABCC2* polymorphisms with resistance to AED are also inconsistent [41]. One meta-analysis suggests that *ABCC2* c.-24C>T polymorphism increases the risk of resistance to AED [42], while another suggests that the recessive model of *ABCC2* G1249A polymorphism could decrease the risk of drug-resistant epilepsy in the Asian population [43]. A recent study showed *ABCC2* c1249G>A polymorphism to be significantly correlated with higher VPA concentration in patients with epilepsy [44].

Also, a recent study suggests an important role for ABCG2 in range modulation of lamotrigine and valproate interactions. Cotreatment with valproate in homozygous carriers of active *ABCG2* 421C>A allele resulted in 2.3-times higher steady-state lamotrigine troughs compared with lamotrigine monotherapy. However, in carriers of low-activity allelic variants, valproate resulted in 5.2-times higher lamotrigine troughs [45].

One study pointed to the possible association of *ABCB1* C3435T genotype and PB concentration in the cerebrospinal fluid (CSF), which resulted in different seizure control. Plasma PB levels were not influenced by C3435T polymorphism, but 3435CC genotype was associated with significantly lower CSF levels of PB and a significantly lower CSF/plasma ratio as compared with CT or TT genotypes. Furthermore, seizure frequency was significantly higher in patients with CC genotype as compared with those with CT and TT genotypes [46].

Many AEDs show pharmacological effects, at least partially, by inhibition of the voltage sodium channels. There are several reports on a significant association of IVS5-91 G>A functional intronic polymorphism in the *SCN1A*gene with phenytoin and CBZ maximum doses and the efficacy of AEDs [47,48], as well as on association of the *SCN1A* and *SCN2A* polymorphisms with the efficacy of VPA [49]. Other studies, however, did not confirm the role of *SCN1A, SCN2A* and *SCN3A* genes in predicting the efficacy of AEDs [50,51]. It should be emphasized that these conclusions may not be applicable to those genetic epilepsies that are caused by specific mutations in sodium channel genes [52].

There have also been studies about possible relationships between AED response and polymorphisms of genes coding for other drug targets such as GABA-A receptor [48], KCNT1 potassium channel [53] and synaptic vesicle proteins SV2A, SV2B and SV2C but there are no clinically relevant conclusions on the investigated polymorphisms [52,54].

## Epilepsy genes

Progress in genomic testing has resulted in identification of a large number of epileptic genes, which account for a large proportion of nonacquired epilepsies. By detecting pathophysiological and molecular mechanisms underlying these epilepsies, the possibilities of individual approach to treatment and selection of drugs that can target these relevant mechanisms are becoming more realistic. Upon identifying the genetic basis of the disease, the treatment can be directed toward correction of specific metabolic defects such as conduction of ketogenic diet for glucose transporter-1 deficiency or pyridoxine use for pyridoxine-dependent epilepsies [55,56]. Knowing the genetic basis of the disease can help in avoiding AEDs that can aggravate the pathogenic defect, such as sodium channel-blocking drugs in Dravet syndrome caused by mutation in *SCN1A*. By selecting a specific AED, the functional disturbance caused by gene mutation can be counteracted, for example, sodium channel blockers in treatment of patients with *SCN8A*-related epilepsy or by selecting retigabine in the epilepsies caused by *KCNQ2*mutation; however, in the meantime, retigabine has been withdrawn from the market [57,58]. However, in the treatment of early-onset epileptic encephalopathy due to glutamate ionotropic receptor NMDA-type subunit 2A (*GRIN2A*) missense mutation (L812M), memantine administration resulted in decreased seizure frequency [57,59].

Better understanding of the pathogenic mechanisms enables development of specifically targeted drugs, such as development of mammalian target of rapamycin (mTOR) inhibitor for the treatment of focal seizures associated with mTORopathy [57].

## The role of genetic variants in ADRs

### Human leukocyte antigen genes

AEDs can cause ADRs, some of which can be severe and life-threatening. A correlation has been reported between *HLA* polymorphisms and the likelihood of ADRs in the form of drug-induced skin injury and drug-induced liver injury [60–62]. Association of the *HLA* allele and hypersensitivity in the form of skin reactions to CBZ, as well as to some other AEDs, including OXC, has been well documented [61–64]. *HLA-B**15:02 is associated with the risk of CBZ-induced cADRs, of which Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are most serious [61]. The population of south-eastern Asia is particularly exposed to this risk because of the significantly higher incidence of risk alleles in this population, unlike the European and Japanese populations. Therapeutic guidelines recommend *HLA-B**15:02 genetic screening as a pharmacogenetic biomarker in individuals of Asian origin prior to CBZ treatment [61]. It has been shown that there is an increased risk of developing SJS/TEN in *HLA-B**15:02 allele carriers when using other AEDs including phenytoin, OXC and lamotrigine [61,64]. *HLA-B**15:02 allele belongs to the HLA-B15 serotype, thus other alleles of the same serotype are associated with an increased risk of SJS/TEN induced by CBZ, but this risk is not as high as for *HLA-B**15:02 allele [61]. *HLA-*

*A**31:01is associated with an increased risk of CBZ-induced cADRs in the Japanese population, as well as in people of European descent [65,66].
It has been shown that routine testing for *HLA-A**31:01 with the aim to reduce the incidence of cADRs in patients prescribed CBZ for epilepsy is a cost-effective use of healthcare resources [67]. *HLA-A**24:02 is also associated with cADRs caused by AED, but the results are inconsistent for lamotrigine, as well as for CBZ and phenytoin [61].

**DNA polymerase-γ gene**

Patients with inherited neurometabolic syndrome are at a higher risk of liver failure induced by VPA due to gene mutations within the mitochondrial *POLG* gene (e.g., Alpers–Huttenlocher syndrome). Therefore, valproate must be avoided in these patients. Furthermore, in children aged less than 2 years with clinical suspicion of this disorder, it is recommended to perform testing for the presence of mutations in the *POLG* gene [68].

**Other nongenetic factors important for treatment of epilepsy**

Since genetic factors account for about 25–50% of all unexpected reactions to a medicinal product, there are other conditions that may affect the efficacy and toxicity of AEDs, such as environmental factors, co-morbidities, other drugs. Some of concomitantly prescribed AED can act as inducers (PB, carbamazepin, phenytoin) or inhibitors (valproate) of metabolic enzymes and drug transporters. Besides, our knowledge of epigenetics as a modulator of drug efficiency is still in the developmental stage [69]. Furthermore, epigenetic modifications and altered structures of chromatin can be induced by AEDs, which may change the course of the disease [70]. Better understanding of these mechanisms of epigenetic influences could result in new targets for improved therapeutic approaches.

**Current state-of-the-art**

Currently, multiple trials are being conducted to evaluate cost–benefits of preventive pharmacogenetic analysis by applying new methodologies. Until recently, common pharmacogenetic polymorphisms have been in focus, and associations with pharmacokinetics or drug-response phenotypes have been estimated. Through this approach, a significant proportion of genetic variability remains undiscovered and unexplained. Although differences in drug exposure are due to genetic predisposition, by testing for common genetic variants we can explain only less than 50% of these genetically encoded variability. Development of sequencing technologies, bring into the focus next-generation sequencing-based methods, like exome and genome sequencing. By applying these methods, rare variants have been detected, which approximately account for 30–40% of the pharmacogenes functional variability, most of which were previously undiscovered [71].
The professional current opinion related to pharmacogenetic testing is as follows: preventive pharmacogenetic testing is limited to confirmed genetic variants, while analysis of all polymorphisms should only be used for retrospective analysis of patients having experienced unpredictable drug reactions.

## Conclusion

Genetic factors contribute to the interindividual variability in patient response to the AED administered. However, genetic testing in predicting the efficacy and toxicity of AEDs is limited and there are only a few examples when such testing can be recommended in routine clinical practice (Table 2) [72]. Genetic influence on AED pharmacokinetics is primarily related to the polymorphism of enzymes involved in AED metabolism. *CYP2C9/2C19* polymorphisms may be relevant in the metabolism/bioavailability of phenytoin, brivaracetam, CLB and partially valproate, as well as barbiturates, while UGT (*UGT1A4* and *UGT2B7*) variants are associated with variable kinetics of lamotrigine and valproate. No reliable gene marker of resistance to AEDs has been identified to date, although there are data suggesting the possible role of *ABCB1* and *ABCC2* gene variants. Gene variants of the *ABCG2* transporter can significantly modulate lamotrigine and valproate interactions. By analyzing several HLA alleles, we can identify high-risk individuals for development of SJS and TEN induced by CBZ, most important of which are *HLAB** 15:02 and *HLA-A**31:01. Also, variant allele carriers have an increased risk in case of the use of OXC, phenytoin and lamotrigine.
Patients with inherited neurometabolic syndrome are at an increased risk of liver failure induced by VPA due to mutations within the *POLG* gene.

## Future perspective

A considerable proportion of genetic variability caused by rare gene variants remains unexplained. Since the significance of rare gene variants on drug pharmacokinetics, drug efficacy and safety has not been extensively evaluated, functional interpretation of these variants represent one of the challenges for the pharmacogeneticists in the future. Next-generation sequencing methodology is a promising, cost-effective approach to personalized treatment applicable in clinical practice. However, there are still many challenges in methodology, specifically in the analysis of genes residing in complex genomic regions, such as HLA, and in result interpretation, along with ethical issues that need to be faced with and resolved before the application of this methodology in pharmacogenomics.
Besides, future studies should deal more comprehensively with the drug–drug–gene interactions which in the case of AED polypharmacy could be very important.

## Executive summary

• Genetic influence on antiepileptic drug pharmacotherapy is proven for variants of: Phase I enzymes (CYP2C9, CYP2C2C19), to be relevant in the metabolism/bioavailability of phenytoin, brivaracetam, clobazam and partially valproate, as well as barbiturates; UGT enzymes (UGT1A4 and UGT2B7), to be associated with variable kinetics of lamotrigine and valproate.
• There are data from some but not all studies suggesting the possible role of ABCB1 and ABCC2 gene variants for
the resistance to antiepileptic drugs.
• Gene variants of the ABCG2 transporter can significantly modulate lamotrigine and valproate interactions.

• HLA-B*15:02 and HLA-A*31:01 are associated with the risk of carbamazepine-induced cutaneous adverse drug reactions. Variant allele carriers have also an increased risk in case of the use of oxcarbazepine, phenytoin and lamotrigine.
• Mutations of the DNA polymerase-γ gene predispose for the liver failure induced by valproic acid.

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**TABLE 1 - Recommended dosing of phenytoin based on *CYP2C9* phenotype/genotype, adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC)(PHARMGKB)**

| **Phenotype** | **Genotype** | **Implication** | **Therapeutic recommendation** | **Classification of recommendation** |
|---|---|---|---|---|
| Extensive metabolizers | An individual carrying two normal activity allels (**1/*1*) | Normal phenytoin metabolism | Initiate therapy with recommended maintence dose. | Strong |
| Intermediate metabolizer | An individual carrying one normal activity allele plus one decreased function allele (**1/*3, *1/*2*) | Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities. | Consider 25% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. | Moderate |
| Poor metabolizer | An individual carrying two decreased function alleles (**2/*2, *3/*3, *2/*3*) | Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities. | Consider 50% reduction of recommended starting maintenance dose. Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response. | Strong |

**TABLE 2 - Table of Pharmacogenomics Biomarkers in Antiepileptic Drug Labeling, adapted from U.S. FOOD & DRUG ADMINISTRATION (FDA) (72)**

| Drug | Biomarker | Labeling text |
|---|---|---|
| Brivaracetam | CYP2C19 | In human subjects possessing one or both mutated CYP2C19 alleles blood level of brivaracetam is increased by 22% or 42%. CYP2C19 poor metabolizers and patients using inhibitors of CYP2C19 may require dose reduction. |
| Carbamazepine | HLA-B | Prior to initiating carbamazepine therapy, testing for HLA-B*1502 should be performed in patients with ancestry in populations in which HLA-B*1502 may be present because of serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), associated with this genotype. |
| | HLA-A | The risks and benefits of carbamazepine therapy should be weighed before considering it in patients known to be positive for HLA A*3101. Moderate association between the risk of developing hypersensitivity reactions and the presence of HLA-A*3101 was found. |
| Clobazam | CYP2C19 | In CYP2C19 poor metabolizers, levels of N-desmethylclobazam, clobazam's active metabolite, will be increased. Therefore, in patients known to be CYP2C19 poor metabolizers, the starting dose should be 5 mg/day and dose titration should proceed slowly according to weight, but to half the dose recommended. |
| Lacosamide | CYP2C19 | There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 poor metabolizers and extensive metabolizers. |
| Oxcarbazepine | HLA-B | Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN. Testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations, prior to initiating treatment with oxcarbazepine. The use of oxcarbazepine should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. |
| Phenytoin | CYP2C9 CYP2C19 | Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant CYP2C9 and CYP2C19 alleles, or drug interactions which result in metabolic interference. |
| | HLA-B | Limited evidence suggests that HLA-B*1502 may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502. |
| Valproic Acid | POLG | Valproic acid is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under two years of age who are clinically suspected of having a mitochondrial disorder. In patients over two years of age who are clinically suspected of having a hereditary mitochondrial disease, valproic acid should only be used after other anticonvulsants have failed. |
| | Nonspecific (Urea Cycle Disorders) | Valproic acid is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders. |