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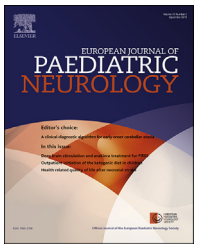

Review article

Efficacy of antiepileptic drugs in the era of pharmacogenomics: A focus on childhood

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ABSTRACT

Background: In recent years advances in the field of pharmacogenomics have expanded the concept for more individualized treatments. Our aim is to provide literature data about the relationship between genetic polymorphisms and efficacy of antiepileptic drugs in children.

Methods: Pubmed was used as the main medical database source. Only original research papers were considered. No year-of-publication restriction was placed. Quality of evidence was assessed according to American Academy of Neurology guidelines.

Results: A total of 12 cross-sectional and case–control studies fulfilled our selection criteria. *ABCB1* gene was associated with drug responsiveness in 2 out of 6 studies and *ABCC2* gene in 1 out of 1 studies. SCN1A gene was also associated with seizure control in 4 out of 5 studies. Cytochrome P450 genes were found to significantly affect drug responsiveness in 2 out of 4 studies, while polymorphisms of uridinediphosphateglucuronosyltransferase*UGT2B7* gene predisposed to drug-resistance in 1 out of 2 studies.

Conclusion: Variability in genes coding for sodium channels, drug transporters and cytochrome P450 enzymes can have a significant impact on response to antiepileptic drugs. Larger prospective studies with better stratification of samples are needed to shed light on these associations.

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1. Introduction

At the crack of dawn of the 21st century the model of precision medicine has shifted the current medical practice from community-based to more individualized management strategies and more targeted therapies.[1] Inter-personal genetic differences can lead to significant heterogeneity of a disease pathogenesis and clinical phenotype, as well as to variability in drugs response (efficacy, safety). In this way, genetics is not only a determinant of predisposition to a disease, but also an emerging determinant of response to antiepileptic treatments.[2]

The challenge now is to translate accumulating genetic discoveries into advances in clinical care and into improvement of life quality of these children. At the same time, ethical issues arise considering the specific features and the vulnerability of a developing organism and demand administration of the most appropriate pharmaceutical substances at the most appropriate dosages.[3]

With regards to epilepsy, genotype–phenotype correlation is not always clear. Variable expressivity, genetic heterogeneity and phenocopies are innate features of most epileptic disorders perplexing the investigation of the genetic basis. However, newly developed tools (e.g. next generation sequencing, whole-exome sequencing) have permitted to identify an increasing number of genes and genetic regions (mainly coding for ion channels, neurotransmitters, neurotransmitters receptors, cell adhesion molecules, neurotrophic factors and factors essential for cytoplasmic processes) whose mutations can predispose or even be the underlying cause of various epileptic disorders.[4,5] On the other side, drug-resistant epilepsy affects ~25% of patients with epilepsy of all ages exerting a negative effect on future neurodevelopment, as well as on their quality of life. It is worth-mentioning that despite the increasing availability of new molecules the aforementioned rate remains unchangeable over years.[6] Although multiple hypotheses have been applied to explain drug-resistant epilepsy, with the *target hypothesis* and *transporter hypothesis* being most cited ones, none of them alone can provide a full pathophysiological background of this phenomenon.[7] The routine practice is to use combinations of antiepileptic drugs to find those with the greatest efficacy and fewer adverse events, while ketogenic diet, surgery or neurostimulation can also be implemented when seizure control is not achieved.[8,9] In parallel, a variety of multisystem dose-related or idiosyncratic adverse reactions may reduce adherence to antiepileptic drugs and consequently negatively affect the response to antiepileptic treatment or even be life threatening.[10,11] Changes in absorption, metabolism, distribution or clearance of a pharmaceutical substance can significantly affect the efficacy of these agents.[12]

Under this view and given the strong genetic background of epilepsy, the study of the role of the genome in antiepileptic drug response prompts investigation, as it could optimize therapeutic choices in this pediatric population. The aim of this review is to provide current sound literature data about the relationship between genetic polymorphisms and the efficacy of antiepileptic drugs in children.

2. Literature search

2.1. *Eligibility criteria*

Studies with the following criteria were selected: 1. original research papers, 2. clinical studies, 3. conducted in pediatric patients with epilepsy, 4. focusing on polymorphisms in antiepileptic drugs related genes,5. including clinical measures of efficacy (i.e. seizure control, proportion of patients with drug-resistant disease)

2.2. *Search strategy and study selection*

A comprehensive search was undertaken by two reviewers independently using Pubmed, Embase, Scopus, Cochrane and Web of Science as the medical database sources. No year-of-publication restriction was placed. The mesh terms that were used were: [“antiepileptic drugs” OR “epilepsy”] AND [“pharmacogenomics” OR “pharmacogenetics” OR “genes” OR “genetics” OR “genetic polymorphisms”] AND [“children” OR “childhood” OR “pediatric”].

After searching the literature, data were abstracted and selected articles were scanned to eliminate studies with irrelevant topic, methodological issues or duplicate records.

2.3. *Quality of evidence*

Quality of evidence provided in each study was assessed according to American Academy of Neurology guidelines.[13] Evidence level ranges from 1 to 4. *Level 1* includes evidence

provided by a prospective study in a broad spectrum of persons with the suspected condition, using a reference (gold) standard for case definition, where test is applied in a blinded fashion (low risk of bias). *Level 2* includes evidence provided by a prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation (moderate risk of bias). *Level 3* includes evidence provided by a retrospective study where either person with the established condition or controls are of a narrow spectrum, and where the reference standard, if not objective, is applied by someone other than the person that performed (interpreted) the test (high risk of bias). *Level 4* includes any study design where test is not applied in an independent evaluation or evidence is provided by expert opinion alone or in descriptive case series without controls. There is no blinding or there may be inadequate blinding. The spectrum of persons tested may be broad or narrow (very high risk of bias).[13]

3. Results

We were able to identify 12 studies fulfilling our inclusion criteria (Fig. 1). Of them 12 investigated the relationship between genetic polymorphisms and efficacy of antiepileptic drugs[14–25] (Table 1). In terms of methodological design our identified papers were case–control or cross-sectional studies. No prospectively designed studies on this topic in pediatric population were found. A total of 6 out of 12 studies had an evidence level of 2 (retrospective study with the use of a control group), while the rest of the studies had an evidence level of 3.

The number of participants in them ranged from 80 to 595. A variety of antiepileptic drugs were used by pediatric patients in the above studies: valproate (5 studies), oxcarbazepine-carbamazepine-lamotrigine (3 studies each), levetiracetam-ethosuximide-clobazam (2 studies each), gabapentin-phenytoin-phenobarbital-gabapentin-topiramate-clonazepam-sultiame (1 study each), while the seizure type included partial (simple or complex) or generalized (tonic, tonic-clonic, atonic, myoclonic, absence) (Table 1). Report of a specific epileptic syndrome was made only in 1 of 12 studies (childhood absence epilepsy). Genes analyzed for potential associations with antiepileptic treatment included ion channel genes, genes coding for drug transporters, cytochrome P450 genes and uridine diphosphate glucuronosyltransferasegenes (Table 2). With regards to origin centers of the studies, 6 of 12 were conducted in European countries, 4 of 12 in countries of Asia, 1 of 12 in America and 1 of 12 in Africa. Significant associations between genetic polymorphisms and aspects of treatment with antiepileptic drugs were identified in 8 out of 12 studies. It should be mentioned that differences among studies in terms of sample size, seizure type and drugs used could introduce significant bias in the interpretation of the results and influence the strength of evidence and should, therefore, be considered when interpreting conclusions.

According to our results, 2 polymorphisms of the gene coding for ATP-Binding Cassette sub-family B, member1 protein (*ABCB1* gene) have been associated with increased risk of resistance to antiepileptic drugs. More specifically, S893A polymorphism (T allele, Ser893Ala) increased the risk of resistance to lamotrigine in a cohort of 446 children with

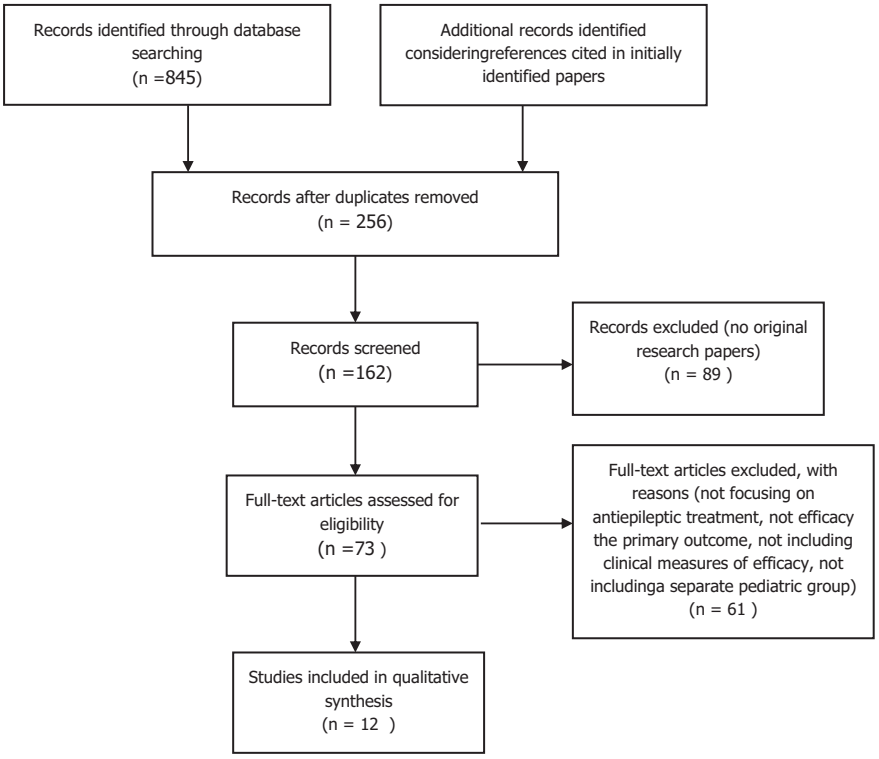

Fig. 1 – Flow-diagram of the selection of articles included in our review.

Table 1 – Studies investigating the impact of specific polymorphisms on efficacy of antiepileptic drugs in children with epilepsy.

Author	Year	Country	Type of the study	Seizure type	Sample	Genes studied	Antiepileptic drugs	Outcome	Evidence Level
Al-Eitan	2018	Jordan	case–control	generalized, partial, generalized myoclonic, generalized tonic-clonic	296 patients VS 299 controls	*KCNA1*, *KCNA2*, *KCNV2*	no data provided	no association between investigated polymorphisms & drug responsiveness	2
Feng	2018	China	cross-sectional	generalized	174 patients	*SCN1A*, *UGT2B7*, *CYP3A4*	valproate	UGT2B7: rs7668282: ↑ risk of drug resistance for the C allele (intron) CYP34A: rs2242480: ↑ remission rate for the T allele (intron) SCN1A: rs10188577: ↑ remission rate for the C allele (intron)	3
Bertok	2017	Slovenia	case–control	generalized, focal, combined focal & generalized	216 patients VS 95 controls	*SCN1A*	valproate, carbamazepine, oxcarbazepine, levetiracetam, lamotrigine, ethosuximide clobazam	G allele (Thr1067Al): ↑ remission rate	2
Glauser	2017	USA	cross-sectional[a]	childhood absence epilepsy	446 patients	*CACNA1G*, *CACNA1H*, *CACNA1I*, *ABCB1*	ethosuximide, lamotrigine, valproate	ethosuximide: CACNA1H rs61734410/ P640L (T allele, Pro640Leu) & CACNA1I rs3747178 (T allele, synonymous mutation) polymorphisms: ↑ the risk of drug resistance lamotrigine: (i) ABCB1 S893A polymorphism: ↑ the risk of drug resistance for the T allele (Ser893Ala) (ii) CACNA1H rs2753326, rs2753325 polymorphisms: ↑ remission rate for the G allele (synonymous mutations) valproate: CACNA1H rs2235634 polymorphism: ↑the risk of drug resistance for the A allele (intron)	3
Margari	2017	Italy	cross-sectional	no data provided	120 patients	*SCN1A*	no data provided	Intronic regions: rs6730344 (A allele), rs6732655 (A allele) and rs10167228 (A allele) polymorphisms: ↑ risk for drug resistance rs1962842 polymorphism (A allele): ↑ risk for drug resistance Exons: no significant associations	3
Abo El Fotoh	2016	Egypt	case–control	generalized, focal, specific epileptic syndrome	130 patients VS 65 controls	*CYP3A5* *3 variant, *SCN1A* gene	no data provided	SCN1A: c.3184 A/G polymorphism: ↑ the risk of drug resistance for the G allele (p.Thr1067Ala) no significant associations for CYP3A5*3 variants	2

(*continued on next page*)

Table 1 – (*continued*)

Author	Year	Country	Type of the study	Seizure type	Sample	Genes studied	Antiepileptic drugs	Outcome	Evidence Level
Uuuik, kkStasiołek	2016	Poland	case–control	no data provided	106 drug-resistant patients VS 67 drug-responsive patients VS 98 healthy controls	*ABCB1*	no data provided	C3435T polymorphism: C allele:↑ the risk of drug resistance T allele: ↑ remission (synonymous mutations)	2
Seven	2014	Turkey	case-controls	generalized, partial	132 patients VS 55 controls	*CYP2C9*, *CYP2C19*, *CYP2D6*	no data provided	CYP2C9: CYP2C9*3 (C allele, Ile359Leu) & CYP2C9*2 (T allele, Cys144Arg): ↑ risk of drug resistance CYP2C19: CYP2C19*2 (A allele, synonymous variant): ↑ risk of drug resistance CYP2D6: no significant associations	2
Seven	2014	Turkey	cross-sectional	generalized, partial	152 patients	*ABCB1*	no data provided	no significant associations with the risk of drug resistance	3
Emich-Widera	2013	Poland	case–control	no data provided	85 patients VS 100 healthy controls	*CYP3A5*, *ABCB1*	carbamazepine, oxcarbazepine, valproate, vigabatrin, clobazam, lamotrigine, gabapentin, phenytoin, levetiracetam, phenobarbital, clonazepam, and topiramate	no significant associations with the risk of drug resistance	2
Ufer	2011	Germany	cross-sectional	generalized, partial	208 patients	*ABCC2*	Carbamazepine + oxcarbazepine, valproate, phenobarbital, Sultiame	ABCC2 1249 variant: ↑ remission (only in patients receiving carbamazepine + oxcarbazepine) for the A allele (Val417Ile)	3
Sánchez	2010	Spain	cross-sectional	partial (simple or complex), secondarily generalized, absence, myoclonic, tonic, tonic-clonic	80 patients	*CYP2C9* & *CYP2C19*, *UGT2B7*, *ABCB1*, *SCN1A*	no data provided	no significant associations with the risk of drug resistance	3

[a] Data was derived from a randomized double-blind trial of ethosuximide, lamotrigine, and valproate but analysis of pharmacogenomic influences was performed in a retrospective way.

Table 2 – Number of studies in which different genes were investigated for potential associations with antiepileptic drugs.

Genes investigated	Number of studies
Ion channels	**KCNA1/KCNA2/KCNV2**: 1 study, **CACNA1G/CACNA1H/CACNA1I**: 1 study, **SCN1A**: 5 studies
Drug transporters	**ABCB1**: 5 studies, **ABCC2**: 1 study
Cytochrome P450	**CYP2C19**:2 studies, **CYP2C9**:2 studies, **CYP3A5**:2 studies, **CYP3A4**:1 study, **CYP2D6**: 1 study
Uridine diphosphate glucuronosyltransferase	**UGT2B7:** 2 studies

absence epilepsy,[18] while C and T alleles of C3435T polymorphism (synonymous mutations) were shown to predispose to more resistant disease in a group of 173 Polish children with epilepsy, but no additional information about antiepileptic drugs used and seizure type was available.[19] In the rest 3 out of 5 studies investigating for effects of *ABCB1* gene on drug responsiveness in pediatric epilepsy no significant associations were revealed.[22,23,25] With regards to ATP-Binding Cassette sub-family C, member 2 (*ABCC2*) gene, it was found to be associated with response to antiepileptic drugs in 1 study conducted in 208 children with epilepsy. In this study the A allele of the 1249G > A variant (Val417Ile) increased remission rate in patients receiving carbamazepine and oxcarbazepine.[24]

Furthermore, in our analysis polymorphisms of voltage-gated sodium channel gene *SCN1A* gene were shown to have a significant impact on drug responsiveness (either positive or negative) in children with epilepsy in 4 out of 5 studies.[15–17,20,25] In these studies the sample size varied greatly from 80 to 216 patients. Genetic variation in T-type calcium channels genes can also predispose to or protect from drug-resistant disease in the study by Glauser et al.[18] with 446 participants, while no associations have been reported for potassium channels.[14]

Finally, in our review polymorphisms of cytochrome P450 genes were found to have a significant impact (either positive or negative) on drug responsiveness in 2 out of 5 studies with a number of participants 174 and 152, respectively.[15,21] Besides, polymorphisms of uridine diphosphate glucuronosyltransferase *UGT2B7* gene were associated with increased remission rate of seizures in 1 out of 2 studies. This study was based on 174 children with generalized seizures[15] (Table 1).

In total, 21 genetic changes were found to be significantly associated with seizure control in our systematic review with 8 out of them affecting introns, 6 being synonymous mutations and 7 leading to amino acid substitution (Table 1).

4. Discussion

4.1. *Drug transporters*

ABCB1 gene (located in chromosome 7, also known as multidrug resistance 1-*MDR1* gene) codes for P-glycoprotein, which is expressed in capillary endothelial cells comprising the blood–brain barrier and acts as an ATP-dependent efflux pump transporting antiepileptic drugs out of the cytoplasm and redistributing them. Overexpression of P-glycoprotein can limit the drug penetration into the Central Nervous System and lead to resistance against antiepileptic drugs that are substrates of this transporter (*transporter hypothesis*).[26,27] Data from studies conducted in adult or mixed populations about the role of *ABCB1* gene in drug-resistant epilepsy is also conflicting withC3435Tbeing one of the most extensively studied polymorphisms.[28–31] A meta-analysis by Lv et al. (2014) revealed that this polymorphism is associated with drug resistance in epilepsy in Caucasian population, whereas Bournissen et al. (2009) in their meta-analysis failed to show any correlation between *ABCB1*genotype and response to antiepileptic treatment.[32,33] An additional interesting finding that should be commented is that the direction of genetic associations is not always the same and different polymorphisms within the same gene may predispose to either drug-responsiveness or drug-resistance, thus reflecting the complexity of interactions between antiepileptic agents and protein-transporters[34]. *ABCC2* gene (located in chromosome 10, also known as multi-drug resistance 2-*MDR2* gene) acts in a similar way and its product couples with ATP hydrolysis to extrude various organic anions out of the cells of the blood–brain barrier. Increased *ABCC2* mRNA expression was reported in brain-derived endothelial cells from patients with drug-refractory epilepsy.[35] Literature data about the pharmacogenomic role of this gene is generally fewer and exhibits discordance; some studies show no significant associations and others have identified polymorphisms as risk factors of drug-resistant disease (especially c.-24C > T polymorphism).[35–37]

4.2. *Ion channels*

Ion channels are essential for the initiation and propagation of action potentials in neurons, which consists the basis of neuronal excitability and epileptogenesis. Many ion channels are the targets of most of the currently available antiepileptic drugs.[38] Mutations in *SCN1A* gene (located in chromosome 2 and coding for alpha subunit of the voltage-gated sodium ion channel) have been well-recognized factors of a various of epileptic disorders (e.g. generalized febrile seizures plus, Dravet syndrome) exhibiting genetic pleiotropy. A series of studies have investigated the relationship of *SCN1A* polymorphism with the risk of drug-resistance (mainly to carbamazepine and oxcarbazepine) in adult patients with epilepsy with mixed results.[39–43] An interesting point that should be highlighted is that the same polymorphism can lead to disease susceptibility, but not necessarily associated with response to treatment.[42] Under this view, synergistic action should not be overlooked and some authors suggest that in fact gene-to-gene or protein-to-protein interactions may be

more important than the independent effects of the polymorphisms of a single gene.[44] In parallel, antiepileptic agents designed to perform their pharmacological action by acting on multiple but non-specific ion channels may finally give genesis to a complex electrophysiological state in the brain.

With regards to other sodium channel alpha subunit genes, few data is available for *SCN2A*and *SCN3A*genes in populations of adult patients demonstrating that some polymorphisms may be associated with drug-resistant epilepsy.[42,45,46] Furthermore, recent studies have shown that potassium and T-type calcium channel genes are involved in pathogenesis of epilepsy and their role as promising targets for epilepsy treatment is also discussed.[47–49] However, their relationship with the development of antiepileptic drug resistance has only been sparsely investigated and acquired data is still controversial.[50,51]

It should be noted that a significant part of differences observed between studies could be attributed to sample size effect, age distribution of cohorts, underlying etiology of epileptic disorder, variance in clinical phenotypes and variance in genotyping methods applied (candidate gene-based, single nucleotide polymorphism-based or haplotype-based approach).

4.3. *Metabolism*

Cytochrome P450 genes and uridine diphosphate glucuronosyltransferase genes are involved in metabolism of most antiepileptic agents strongly affecting their distribution, action, excretion and other parameters of pharmacokinetics and in this way they can exert an influence on their final efficacy in seizure control.[52]

Proteins belonging to the superfamily of P450 are the major enzymes involved in drug metabolism, accounting for about 75% of the total metabolism. Several isoenzymes have been studied for their potential relationship with antiepileptic drug resistance. Genetic variance in *CYP3A4* gene (located in chromosome 7) has been correlated with differential activity and altered kinetics mainly in (pediatric and adult) patients receiving carbamazepine.[53–57] In the study by Feng et al. (2018) included in our analysis the T allele of the polymorphism rs2242480 was found to be associated with better seizure control in children with generalized seizures receiving valproate.[15] On the contrary, we were not able to identify studies in pediatric populations showing any associations between variants of *CYP3A5* gene (chromosome 7) and response to antiepileptic treatment.[20,23] In general, the role of this isoenzyme is not so thoroughly studied, although Park et al. have demonstrated an effect of CYP3A5*3 genotype on serum concentrations of carbamazepine.[58]

A significant number of papers about the effect of variants of *CYP2C9* and *CYP2C19* genes on metabolism of antiepileptic drugs (especially valproate, phenytoin, phenobarbital) are available in literature. In general, studies in adult and pediatric patients have revealed that *CYP2C9*2* and *CYP2C9*3* alleles are associated with slower metabolism of phenytoin so that patients carrying at least 1 allele need lower therapeutic doses.[59–61] Moreover, the prevalence of *CYP2C9*3*seemed to be significantly lower among patients exhibiting drug-resistance.[62,63] Similarly, carriers of *2 or *3 alleles of *CYP2C19* gene seem to be slower metabolizers of various antiepileptic drugs and usually exhibit a higher concentration-to-dose ratio.[53,59,64] Seven et al. (2014) in their study, which is included in the results of our analysis, did not confirm the aforementioned findings.[21] There are additional studies in literature failing to demonstrate any association of CYP2C9 or CYP2C19 variants with pharmacokinetics of specific antiepileptic drugs.[65–68] It should also be noted that slower metabolism may be associated with more side-effects. Indeed, *3 allele of *CYP2C9*and *2 allele of *CYP2C19* seem to increase the risk of severe cutaneous reactions in children induced phenytoin and phenobarbital, respectively, while loss-of-function alleles of *CYP2C19* are associated with valproate-induced weight gain.[69–71] *CYP2C19* catalyzes testosterone to form androstenedione and progesterone to hydroxyprogesterones. A high level of testosterone may induce the accumulation of abdominal fat, while in the presence of estrogen, progesterone stimulates appetite and promotes weight gain.[71] In this way, the effect of loss-of-function mutations of *CYP2C19* on hormone profile can aggravate one of the most known adverse effects of valproate (weight gain), although valproate is not a substrate of *CYP2C19*. All these results are particularly important, as the appearance of side-effects can reduce adherence to treatment and has eventually a negative effect on efficacy of antiepileptic drugs. *CYP2D6* gene has also been analyzed in the study by Seven et al. (2014), but no associations with clinical measures of antiepileptic drugs efficacy were identified. In literature López-García et al. (2017) had shown that *CYP2D6*2* and*CYP2D6*4* alleles lead to decreased activity of cytochrome P450 in a group of children with epilepsy receiving valproate, lamotrigine, levetiracetam, phenytoin and carbamazepine, although the authors of this paper do not provide a pathophysiological background.[53] An interesting aspect is that in the paper by Runtz et al. (2018); seizure activity could modify the cytochrome P450 expression in the liver and the hippocampus.[72] Furthermore, according to Hřebačková et al. (2009), valproate (a histone deacetylase inhibitor) seems to induce the expression of *CYP3A4* in neural tissues.[73] Taking these findings into account one could speculate that specific polymorphisms of the genes coding for these enzymatic systems could make them more "vulnerable" to the effects of epilepsy and antiepileptic drugs. On the other hand, we cannot definitely rule out the possibility that these findings are due to relatively small study samples and have no clinical significance. In any case, the afore mentioned correlations need to be confirmed in future studies.

Uridine diphosphate glucuronosyltransferases are enzymes responsible for the process of glucuronidation, a major part of phase II metabolism of drugs, which is determinant for the excretion of the drug through kidneys.[74] *UGT2B7* (chromosome 4) is considered to be a highly polymorphic gene and various studies have investigated the potential effect of these polymorphic variants on glucuronidation activity and on pharmacokinetics of antiepileptic drugs.[75] According to their results, C-161T polymorphism seems to exert an influence on lamotrigine metabolism and increase its concentration-to-dose ratio.[64,76,77] Wang et al. have also identified a similar effect of this polymorphism on valproate metabolism in children with epilepsy, which was enhanced by lamotrigine co-administration.[78] Besides, a recent meta-analysis

demonstrates significant effects of *UGT2B7*gene on valproate pharmacokinetics and pharmacodynamics.[79] Nevertheless, not all available studies confirm these associations.[65,80,81] In terms of clinical outcomes in children with epilepsy we were able to identify 1 study revealing a negative effect of polymorphism rs7668282 of *UGT2B7*gene on response to antiepileptic drugs.[15] Studies about associations of *UGT1A4* and *UGT1A6* polymorphisms with lamotrigine and valproate metabolism are also available, but we have identified no data with regards to their clinical effect in children with epilepsy.[65,80,82]

We ought not to omit to comment that a significant number of genetic changes significantly associated with disease control were silent mutations (synonymous) or affected noncoding DNA sequences (introns). Indeed, accumulating evidence from genome-wide association studies, has revealed a substantial contribution of synonymous single nucleotide polymorphisms to human disease risk and other complex traits. More specifically, they give genesis to new binding sites for transcription factors and other DNA binding proteins and hence affect the expression of other genes or they may create homology between sequences and can result in recombination and chromosomal translocation between similar alleles. Furthermore, they have been shown to alter the folding of proteins, as well as programmed translational speed. At the same time mutations in introns can alter splicing patterns and influence activity and stability of protein products.[83,84]

Analysis of all the aforementioned studies presents a series of *limitations*. Variability in age, sample size, seizure type and phenotype definition consist potential confounding factors. An additional significant drawback is that in the majority of them (7 out of 12) no specific data about the combination of antiepileptic drugs administered is provided and patients are considered as a single group instead of being stratified according to the agents they receive. This is particularly important for studies investigating the effect of *ABCB1* gene, as P-glycoprotein does not exhibit the same specificity for all its substrates.[85] Moreover, there have been described mutations that selectively affect the interaction of P-glycoprotein with specific drug substrates, while total levels of the protein remain unchangeable. Besides, as several epilepsy pharmacogenomic studies include children alongside adults, stratification by age would undoubtedly add to the available pediatric evidence base. At the same time the definition of drug-resistant epilepsy used is not consistent between different studies. This fact undoubtedly reduces the credibility of the findings and introduces bias in the interpretation of the results. Finally, as all aforementioned studies have been conducted in different populations, one should consider the fact that the prevalence of specific variants/alleles may differ significantly between ethnic groups.

5. Future directions

Pharmacogenomics is increasingly becoming popular both in an academic and in an industrial level. However, despite the growing body of research, available data often exhibits discrepancies, definite conclusions are missing and lack of replication remains a critical issue. This fact may reflect underlying limitations in methodology and design.[86,87] Moreover, changes in drug metabolism and pharmacokinetic parameters cannot always be directly translated into changes in therapeutic response and seizure control. The challenge for future research on this topic is to combine new discoveries with appropriate implementation of evidence-based guidelines and strategies in the clinic.

For this purpose more prospective studies based on larger samples are needed to provide results with greater statistical power. Larger samples permit better stratification and also increase the power of pharmacogenomic studies to investigate and identify the effect of less common variants on seizure control, as well as on adverse drug reactions. Funding of larger studies is an important aspect and opportunities for financial resources include grants, scholarships or funding from National Institutes. As resources may not be always available, pooling of biobanks should also be considered. In parallel, given the heterogeneity and complexity of epilepsy pathogenesis, it would be useful for future studies to focus on well-characterized (clinically or phenotypically) groups of patients or even stratify participants according to their specific traits (e.g. epileptic syndrome, etiology of epilepsy: genetic-structural-metabolic, antiepileptic drugs used). In this way, novel genetic associations could be more easily and accurately interpreted and implemented into clinical care. However, as patients with drug-resistant disease use a variety of antiepileptic drugs with different modes of action, adjustment for this confounding factor is not always feasible. Stratification by age is also needed, as etiology of epilepsy presents remarkable differences in different age groups and at the same time pharmacological traits of a developing organism can significantly change with maturation. For the same reason conduction of pharmacogenomic studies in pure pediatric populations is essential, too. Furthermore, as ethnologic background has an essential role in the demography of genetics and distribution of different polymorphisms, recruitment of participants of different nationalities would help in analysis and generalization of results.

On the other side, the use of pharmacogenomic tests should be harmonized with applied policies for conventional drugs and procedures. This presupposes appropriate education of clinicians and other health care practitioners, as well as assignment of special hospital or institutional committees.[88–90] Pilot programs have already successfully advanced the use of pharmacogenomics in the field of drug safety and pharmacovigilance.[91] Besides, outcomes of these processes should be systematically monitored and recorded and benefit-cost analyses need to take place at regular intervals to assess cost-effectiveness of pharmacogenomic tests.[92]

6. Conclusion

Precision medicine principles and pharmacogenomics have begun to integrate into pediatric clinical practice and promise to optimize treatment options maximizing efficacy and reducing side-effects. In the field of childhood epilepsy results from recent research have identified considerable

associations between variability in a series of genes and aspects of responsiveness to and metabolism of antiepileptic agents. Nevertheless, challenges still exist with regards to incorporation of this accumulating genetic information into routine screening procedures and into current therapeutic protocols, thus bridging pediatric practice with basic research. In any case, larger studies including more homogenous groups of children with epilepsy and considering special pharmacological characteristics of a developing organism are anticipated to further confirm the role pharmacogenomics can play in the management of these patients.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.06.004.

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