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Pharmacogenetics of antiepileptic drugs: A brief review

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Abstract

The goal of pharmacogenetic research is to assist clinicians in predicting patient response to medications when genetic variations are identified. The pharmacogenetic variation of antiepileptic drug response and side effects has yielded findings that have been included in drug labeling and guidelines. The goal of this review is to provide a brief overview of the pharmacogenetic research on antiepileptic drugs. It will focus on findings that have been included in drug labeling, guidelines, and candidate pharmacogenetic variation. Overall, several genes have been included in guidelines by national and international organizations; however, much work is needed to implement and evaluate their use in clinical settings.

Keywords: pharmacogenetics, antiepileptics, review

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Introduction

The goal of pharmacogenetic research is to utilize genetic information in order to aid in treatment selection and monitoring.[1] It is also thought to be a potential source for biomarker discovery. Knowledge gained from pharmacogenetic studies could be utilized in clinical settings for precision or personalized medicine. The use of precision medicine by the clinician may one day enable clinicians to deliver pharmacotherapy with a priori knowledge of how the patient will respond (positively and negatively); however, many barriers still exist to accomplishing this goal.[2] Considerable amounts of research have gone into predicting drug response in various disease states through the genetic variation that may influence the pharmacokinetics and pharmacodynamics of medications. Fields such as cancer and cardiovascular disorder have seen great growth in the discovery and application of pharmacogenetic findings to patient care.[3,4] Research in psychiatric and neurologic pharmacogenetics has also progressed rapidly with many findings; however, to date, few are implemented in the clinic and available on genetic screening panels.[5,6] Due to the high number of patients who do not respond to a given antiepileptic drug (AED), pharmacogenetic research in this area continues to evolve.[7] Epilepsies can occur secondary to many causes (eg, febrile seizures, traumatic brain injury). For epilepsies that may arise to due genetic predisposition, these are likely a complex trait that is not due to a single genetic factor. This may account for the inconsistent findings in identifying genetic variation associated with AED efficacy.[8] In contrast, several strong associations have been identified between AED use and side effects. This review provides a brief overview of the pharmacogenetic findings of AEDs with an emphasis on replicated and/or clinically actionable findings. As such, only a few AEDs will be reviewed. A comprehensive review of all AED pharmacogenetic research can be found elsewhere.[9-11]

Pharmacokinetics

Pharmacokinetics refers to the action of the drug on the body and includes absorption, distribution, metabolism, and excretion. The majority of pharmacogenetic work

TABLE: Summary of *CYP2C9* pharmacogenetic guideline recommendations for phenytoin

CYP2C9 Metabolizing Status[a]	CPIC Guidelines Recommendation[15]	DPWG Recommendation[16]
Ultrarapid	N/A	N/A
Extensive	Use recommended package insert maintenance dosing	N/A
Intermediate	25% reduction in initial maintenance dose	Standard loading dose followed by 25% reduction in maintenance dose. Evaluate levels after 7 to 10 days
Poor	50% reduction in initial maintenance dose	Standard loading dose followed by 50% reduction in maintenance dose. Evaluate levels after 7 to 10 days

CPIC = Clinical Pharmacogenetics Implementation Consortium; *CYP2C9* = cytochrome P450 2C9; DWPG = The Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group.

This table describes the pharmacogenetic guidelines for HLA-B*1502 noncarriers based on *CYP2C9* metabolizer status. If the patient is a carrier of HLA-B*1502, then alternative therapy should be considered. Following initial dose, the clinician should continue to manage and adjust dosing based on levels and clinical response.

[a]Several alleles can fall within each metabolizer status. Please consult the supplementary information of the CPIC guidelines for further information regarding *CYP2C9* alleles and metabolizer status.

with AEDs has been done in the phase I metabolizing cytochrome-P450 (CYP) enzyme system.[12] Overall, several CYP isoenzymes are thought to be involved in the metabolism of AEDs, which, depending on the particular drug, could lead to either activation or deactivation of the AED. The efficiency of a CYP enzyme to metabolize a given drug can be influenced by interindividual genetic variation, and an individual's CYP enzyme status is categorized as ultrarapid, extensive (considered the normal homozygous wild type), intermediate, and poor metabolizer.[13] Intermediate and poor metabolizers carry 1 or 2 deficient alleles, respectively, and have a slower rate of metabolizing compared to the extensive metabolizers. An ultrarapid metabolizer has multiple gene copies and a higher rate than that of extensive (normal) metabolizers.[14] Thus, the particular type of CYP genetic variation a person has can have substantial influence on their ability to metabolize a given medication.

CYP2C9

In 2014, the Clinical Pharmacogenetics Implementation Consortium (CPIC) published guidelines on the use of *CYP2C9* pharmacogenetic testing in phenytoin dosing.[15] These guidelines state that, after accounting for clinical characteristics, patients who are found to be extensive metabolizers do not need a dose adjustment of their phenytoin (or fosphenytoin). This applies to the majority of patients as approximately 91% of the population are *CYP2C9* extensive metabolizers. The guidelines do recommend at least an initial maintenance dose reduction of 25% for patients that are intermediate metabolizers (~8% of the population). Likewise, patients that are *CYP2C9* poor metabolizers should receive at least a 50% dose reduction. Continued adjustment of maintenance dosing should be based on therapeutic drug monitoring and patient response. The Dutch Pharmacogenetics Work Group (DPWG) also released recommendations for dosing of phenytoin based on *CYP2C9* metabolizer status in 2011.[16] Overall, the CPIC and DPWG guidelines agree in their dosing recommendations of phenytoin based on *CYP2C9* (Table). We encourage the reader to consult the CPIC guidelines for an in-depth review of the guidelines because they are the most recent, peer-reviewed recommendations available for phenytoin *CYP2C9* pharmacogenetic-based dosing. Phenytoin's package labeling does include a reference to genetically determined metabolizing status; however, no specific recommendations are included.[17]

Permeability Glycoprotein

Permeability glycoprotein (Pgp) or multidrug resistance protein 1 is an efflux protein pump that lines the blood-brain barrier.[18] The gene encoding Pgp is the ATP-binding cassette subfamily B member 1 (*ABCB1*) gene.[19] To date, *ABCB1* findings have not been included in drug labeling likely due to a lack of replicated findings; however, there appears to be some evidence behind this gene's influence on phenytoin and carbamazepine levels. The haplotype containing the *ABCB1* rs1045642 variant, which encodes a silent polymorphism at exon 26, and the *ABCB1* rs1128503 variant, encoding for a synonymous mutation in exon 13, which are in linkage disequilibrium, was associated with altered phenytoin levels in a Black Beninese population.[20] Within this study, the subjects with the AA genotype showed elevated 4-hour levels of phenytoin after a single 300-mg dose. The *ABCB1* rs1045642 G allele was also found to be associated with phenytoin resistance in a population of subjects of Egyptian descent.[21] This effect

on phenytoin levels or AED response for the rs1045642 variant was not able to be replicated in a healthy control, European ancestry population, or in a population of subjects of North Indian descent.[22,23] Similarly, studies have consistently shown no effect of *ABCB1* rs1045642 on carbamazepine levels.[23-25] An alternate variant in *ABCB1*, rs2032582, was initially associated with lower carbamazepine levels but was not replicated in several other cohorts.[23-25]

Studies have also looked at the *ABCC2* gene, which encodes the multidrug resistance protein 2 transporter (another member of the ATP-binding cassette family). The *ABCC2* gene is predominately expressed in hepatocytes and functions in biliary transport. As with the *ABCB1*, *ABCC2* initially found an association with carbamazepine and oxcarbazepine response in Caucasian patients treated for epilepsy; however, this was unable to be replicated in follow-up studies.[24,26-30]

Although variants of the Pgp system are likely candidates for pharmacogenetic response to several AEDs, work has yielded mixed results, and thus, these findings cannot yet be implemented in the clinic setting. Further work is needed in well-defined populations in order to fully understand the genetic contribution of this complicated family of proteins in AED outcomes.

Pharmacodynamics

AEDs have many potential candidate genes for study in relation to their pharmacodynamics interactions with ion channels, receptors, transporters, and other proteins.[31] Some of the strongest pharmacogenetic evidence to date has come from the pharmacodynamics of AEDs.

Human Leukocyte Antigen

The human leukocyte antigen (HLA) system is a group of genes on chromosome 6 that encode for cell surface proteins involved in the regulation of immune response.[32] Of the 3 major histocompatibility classes, class I (which includes subtypes A, B, and C) has been the subject of the majority of the pharmacogenetic research of AED side effects, namely, cutaneous reactions in the form of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[33] *HLA-B* genes are some of the most polymorphic genes in the genome with more than 2000 alleles.[34] To aid in the understanding and uniformity of *HLA* genes, the World Health Organization Nomenclature Committee for Factors of the HLA System was formed and can be accessed online (http://hla.alleles.org/). To date, *HLA-B* genetic information has been included in the guidelines and/or the drug labeling for phenytoin and carbamazepine.

The *CYP2C9* phenytoin recommendations made by CPIC (described above) are based on the patient's overall HLA-B*1502 carrier status.[15] The guidelines are broken down by genotypes, HLA-B*1502 carriers and HLA-B*1502 noncarriers. Due to the repeated association of the HLA-B*1502 allele with a substantially increased risk of phenytoin-induced SJS/TEN, the guidelines state that if a patient is found to be a carrier of this allele then other therapies should be used. Thus, the *CYP2C9* recommendations (above) for phenytoin do not apply if a patient is a HLA-B*1502 carrier. The *CYP2C9* recommendations only apply for noncarriers of this allele. This same recommendation for HLA-B*1502 status applies for carbamazepine and is reflected in its package labeling and CPIC guidelines.[35,36] Although in most circumstances these medications should be avoided if a patient is HLA-B*1502 positive, one may cautiously consider their use if the patient has previously received the drug for longer than 3 months without incident. Because SJS/TEN generally occurs within 3 months of drug initiation, these patients are at a lower risk for developing this life-threatening reaction. However, the risk is never completely eliminated, so patients should be monitored closely for any new cutaneous developments throughout therapy.

The frequency of occurrence of the HLA-B*1502 allele is considerably higher in patients of Asian descent and, in particular, Han Chinese. The FDA recommends genetic testing prior to initiation of carbamazepine or phenytoin therapy in these high-risk populations. A meta-analysis has estimated that the HLA-B*1502 allele significantly increases the risk of SJS/TEN by anywhere from 25- to 220-fold, depending on the particular Asian race/ethnicity.[37] In other populations, such as Caucasians, the frequency of the *1502 allele is much lower but can be present. Thus, a careful assessment a patient's family history, including family lineage, should occur in order to assess the usefulness of genetic testing before starting AED treatment.

In a recent addition to the boxed warning regarding *HLA-B*, carbamazepine also contains a warning for increased risk of SJS/TEN with a genetic variant in the *HLA-A* gene. This warning is from replicated findings in patients of European, Korean, and Japanese ancestry for whom the HLA-A*3101 allele resulted in a substantially increased risk of drug-induced hypersensitivity including SJS.[38] Estimates for the increased risk of drug-induced hypersensitivity for populations carrying the *3101 allele range from 5% to 26%. The *3101 is found in 2% to 5% of patients with Northern European descent and at even higher levels in patients of Japanese descent.[39-41] Despite the *3101 allele not currently being included in carbamazepine pharmacogenetic guidelines, this increased risk has led the FDA to expand carbamazepine's labeling to include monitoring and caution for SJS/TEN in patients that carry

the HLA-A*3101 allele. This strong association will likely be added to an updated pharmacogenetic guideline of carbamazepine in the future.

Urea Cycle Disorder Enzymes

Urea cycle disorders result from deficiencies in the enzymes that encompass the urea cycle pathway. The pathway is key for the metabolism and clearance of nitrogenous waste. In-depth reviews of urea cycle disorders can be found elsewhere.[42,43] As much as 50% of neonates with elevated ammonia, resulting from urea cycle disorders, have seizures.[44-46] Valproic acid carries a black box warning contraindicating its use in patients with urea cycle disorders due to the risk of valproic acid–induced hyperammonemic encephalopathy. The true mechanism behind the hyperammonemia caused by valproic acid is still unknown; however, research has focused on abnormalities with the urea cycle.[47-50] Interestingly, valproic acid has been known to uncover later-life urea cycle disorders due to its ability to accumulate ammonia in patients carrying genetically mild urea cycle disorders beyond that of what may be expected from valproic acid alone. A review of the specific genetic mutations in urea cycle disorders is beyond the scope of this review but can be found elsewhere.[51] Currently, genetic testing for urea cycle disorders is still uncommon as most diagnoses are made based on clinical symptoms. In the future, wide-scale prenatal genetic testing may become commonplace, and so an understanding of the genetic basis for this adverse drug event is necessary to direct treatment.

Mitochondrial Disease

Valproic acid contains a boxed warning against its use in populations with known hereditary neurometabolic syndromes, such as Alpers Huttenlocher syndrome. These syndromes are caused by abnormal function in the polymerase DNA directed gene (*POLG*) on chromosome 15, which can potentially be caused by many different genetic mutations.[52] Alpers Huttenlocher syndrome, just one of the *POLG*-related disorders, is characterized by seizures, psychomotor regression, and liver disease.[53] The most common *POLG* mutation found in more than two thirds of all *POLG*-related disorders is caused by an exchange of an alanine amino acid for a threonine at position 467 (Ala467Thr).[54] This mutation disrupts the formation of the DNA polymerase protein, reducing its ability to make DNA. The use of valproic acid in patients with any form of a *POLG* mutation or patients under 2 years of age suspected of having a mitochondrial disease is contraindicated as it may cause acute and fatal iatrogenic liver injury.[55] It is thought that the liver toxicity seen with valproic acid is secondary to its interruption of fatty acid oxidation in the mitochondria. Patients with mitochondrial disease are at increased risk for liver toxicity as they carry inborn errors of fatty acid oxidation in the mitochondria. Thus, this pharmacogenetic knowledge in the management of Alpers Huttenlocher and other *POLG*-related disorders is essential to preventing adverse outcomes from valproic acid therapy.

Voltage-gated Sodium Channels

The exact mechanism of action of AEDs is not fully understood and may vary from drug to drug. It is thought that the voltage-gated sodium channels are one of the major targets for several AEDs, including phenytoin, carbamazepine, and lamotrigine.[56] Valproic acid acts on voltage-gated sodium channels indirectly through the GABA system.[57] The voltage-gated sodium channels are made up of several subunits, and at least 1 alpha subunit is needed to have a functional channel.[58] Pharmacogenetic research has looked at a series of genes on chromosome 2 that encode these sodium channel alpha subunits (*SCNA*). A considerable amount of work has investigated AED response based on the genetic variation of 3 specific subunits—*SCN1A*, *SCN2A*, and *SCN3A*—which are highly expressed in the brain.[59] Findings to date have been inconsistent. The inconsistent findings could be due to several factors, including polypharmacy, drug-drug interactions, and ethnicity. A recent, large, multicenter trial followed by a meta-analysis investigated the association of several candidate variants from the *SCN1A*, *2A*, and *3A* genes with either carbamazepine or valproic acid monotherapy in patients of Asian descent.[60] The authors found no effect of *SCNA* variants on AED response in either their trial or their follow-up meta-analysis. Despite this negative finding, other studies have found significant relationships between AED response and *SCN1A* and *SCN2A* variants for carbamazepine and phenytoin,[22,24,61] Thus, it remains unclear whether genetic variation of the *SCNA* genes could be potentially useful in certain subpopulations or specific drugs, and future work will be needed to translate these findings for clinical use.

Epoxide Hydrolase 1

Microsomal epoxide hydrolase is an enzyme that metabolizes xenobiotics by making reactive epoxides into water-soluble compounds for excretion.[62] Carbamazepine is metabolized into its active form, carbamazepine-10,11-epoxide, which is then deactivated by microsomal epoxide hydrolase and excreted.[63] Genetic variation at 2 sites, rs1051740 and rs2234922, of the gene that encodes microsomal epoxide hydrolase I (*EPHX1*) have been associated with altered carbamazepine levels. CC carriers of the rs1051740 genotype and GG carriers of the rs2234922 may require decreased doses of carbamazepine as studies have shown that they may have higher levels compared to noncarriers.[24,64,65] Due to the possible

correlation of AED dose and teratogenic effects, these same variants of *EPHX1* have been associated with phenytoin-induced craniofacial abnormalities in mothers that were treated with phenytoin.[66,67] Carriers of the rs2234922 AA were found to have a lower but present risk of having a child with craniofacial abnormalities compared to noncarriers if they had received phenytoin during pregnancy. The authors speculate that this protective genetic effect may arise from the decreased amount of teratogenic reactive oxide formation during phenytoin's metabolism. Findings from both the carbamazepine and phenytoin studies are promising and may one day be incorporated into AED guidelines. Replication in prospective formats is needed before this will occur.

AED Pharmacogenetics in Patient Care

Pharmacogenetic research will undoubtedly continue to add to the existing body of evidence. Guidelines and references are available to assist in understanding this work and include The Pharmacogenomics Knowledgebase (pharmgkb.org), the CPIC guidelines, the DPWG, and the Canadian Pharmacogenomics Network for Drug Safety (cpnds.ubc.ca). Pharmacists will be an integral part of understanding this data and aiding in its application to patient care. Indeed, this is taking place as pharmacogenetics is becoming increasingly more common in the clinic with the rates of insurance reimbursements increasing and work being done to compare conventional treatments to pharmacogenetic-aided or -directed treatment strategies.[68,69] Furthermore, the ability to obtain genetic information from patients is becoming easier, less expensive, and more rapid as technology advances. It will be essential for current and future generations of pharmacists to have an understanding of pharmacogenetic principles and their application to patient care. This is being reflected in the curriculum of many pharmacy schools, and in the future, specialty training in pharmacogenetics may be required to assist in the implementation of precision medicine through the use pharmacogenetics.[70,71] Ultimately, pharmacogenetic information will never override clinical assessment of the patient but rather add another important piece of information that the treating clinician will be required to synthesize and weigh when determining treatment goals.

Along with the ability to analyze and use genetic information to direct treatment strategies, there will come ethical considerations in patient information and protection. Although federal law prohibits discrimination based on genetic information in most forms (with the exception of life, disability, and long-term care insurance), clinicians will need to be sensitive to the privacy of genetic information and the possible implications of a genetic finding outside of its originally ordered purpose. Further information can be found at the National Coalition for Health Professional Education in Genetics (NCHPEG: http://www.nchpeg.org). The classic example of this is with the APOE gene. Although a clinician may order the APOE genetic test for lipid management, it is also a known risk factor for Alzheimer's disease, and so this must be taken into account when interpreting the results and reporting them to the patient. Patients may have a lack of knowledge of how their genetic information could be used and should be protected, and so we must work to empower and educate them on their genetic information.

Conclusions

The pharmacogenetics of AEDs has had several promising findings that can aid providers in improving therapeutic regimens. Further work is needed to implement these findings in the clinic. Ultimately, the pharmacist may play a role to aid providers in interpreting and implementing genetic information to improve patient care.

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