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Biomarkers for antiepileptic drug response

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Abstract

The identification and validation of genetic factors ('biomarkers') that reliably predict the efficacy and toxicity of specific pharmacological agents for individual patients would significantly improve the current treatment of patients with epilepsy. A pharmacogenetic biomarker classification has been proposed that identifies three biomarker types involved in drug response: 'known valid biomarkers', 'probable valid biomarkers' and 'exploratory or research biomarkers'. The only known valid antiepileptic drug biomarker is *HLA-B*1502* (Stevens-Johnson syndrome in patients of specific Asian backgrounds taking carbamazepine). Probable valid antiepileptic drug biomarkers include polymorphisms in one drug transporter gene, two drug metabolizing genes, three sodium channel genes and one HLA allele. Current methodological challenges to identifying new antiepileptic medication biomarkers can only be overcome with large-scale collaborative research efforts.

Keywords

ABCB1; antiepileptic drug; biomarkers; CYP2C19; CYP2C9; *HLA-A*3101*; *HLA-B*1502*; *MDR1*; multidrug-resistance gene 1; *PGY1*; pharmacogenetics

The current treatment of epilepsy involves using antiepileptic drug (AED) efficacy, tolerability and safety population data to select a medication followed by a 'titration to clinical response' approach to find the patient-specific dose. Due to marked interindividual variability in AED response, this approach often results in excessive adverse events coupled with delays in reaching the therapeutic goal of 'no seizures, no side effects'. Each patient's clinical response represents the outcome of drug–patient interaction – a delicate interplay between pharmacokinetics and pharmacodynamics [1]. Theoretically, multiple genetic and nonheritable factors have the potential to differentially impact on this pharmacokinetic/pharmacodynamic drug–patient interaction. The identification and validation of genetic and nonheritable factors ('biomarkers') that reliably predict the efficacy and toxicity of specific pharmacological agents for individual patients would significantly improve the current treatment of patients with epilepsy by increasing the chance of selecting earlier the most efficacious, least toxic AED for that specific patient. This would lessen the time to seizure freedom, reduce the risk of life threatening or intolerable side effects and decrease the cost to both patients and the healthcare system [2].

Based on the relationships identified above, a common approach for classifying biomarkers has been by their effect on either pharmacokinetic pathways or pharmacodynamic actions. Although conceptually sound, this mechanistic approach does not systematically address the key issue of clinical relevance. By contrast, the US FDA proposed a pharmacogenetic biomarker classification based on reliability, scientific evidence and clinical relevance [101]. Although not perfect, it provides a useful framework for evaluating potential AED biomarkers.

This regulatory classification identifies three biomarker types involved in drug response: 'known valid biomarkers', 'probable valid biomarkers' and 'exploratory or research biomarkers' [101]. A known valid biomarker is defined as "A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic or clinical significance of the results" [101].

A probable valid biomarker is defined as "a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic or clinical significance of the test results. A probable valid biomarker may not have reached the status of a known valid marker because, for example, of any one of the following reasons:

- The data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny;
- The data elucidating its significance, although highly suggestive, may not be conclusive;
- Independent verification of the results may not have occurred" [101].

Exploratory or research biomarkers are identified from research that is "intended to facilitate global analysis of gene functions, but not specific claims pertaining to drug dosing, safety assessments, or effectiveness data" [101] or research whose results do not fulfill the criteria for a known or probable valid biomarker.

The FDA classification schema is focused on pharmacogenetic biomarkers. As such, nonheritable factors (e.g., seizure type, age, weight, concomitant medications and concurrent hepatic or renal disease) that clearly have recognizable effects on AED pharmacokinetics and pharmacodynamics [3] have not been classified using this approach. However, it would be reasonable to propose that the key known valid nonheritable biomarker for all AEDs would be seizure type while probable valid biomarkers for some AEDs could include specific concomitant medications and concurrent hepatic or renal disease.

It is reasonable to apply this FDA classification to the major sources of biological variability: differences in DNA, RNA, proteins and endogenous/drug metabolites [2]. In general, DNA variability can take many forms including single nucleotide polymorphisms, deletions or insertions of at least one DNA base (often hundreds or thousands), or deletions or insertions of repetitive DNA [4]. In addition to structural variability in DNA, differences in the transcription of DNA into mRNA (with resultant changes in the expression and synthesis of key proteins) along with differences in protein activities and interactions in complexes can produce interindividual variability in drug response [2]. Lastly, both endogenous and exogenous (occurring as a result of drug metabolism) small molecules can impact drug response [4,5]. This last group of biomarkers are studied in the field of metabolomics, also called metabonomics, which focuses on the quantitative analysis of metabolites [6].

Overall, the science of identifying DNA, RNA, proteins and metabolite biomarkers for AED response remains in its infancy; future growth and development in this area is challenged by methodological and technical issues. This article will use the FDA regulatory classification to examine genetic or metabolomics AED biomarkers and examine epilepsy-specific methodological issues critical to identifying and validating future AED biomarkers. The AED known valid biomarkers discussed are those identified by the FDA; the probable valid and exploratory/research biomarkers were classified by the author.

Known valid AED biomarkers

*HLA-B*1502* (for Stevens–Johnson syndrome)

Several studies have demonstrated an association between carbamazepine-induced Stevens–Johnson syndrome and *HLA-B*1502* in subjects from China, Thailand and Malaysia but not in subjects from either Europe or Japan [7,8]. In the high-risk populations, linkage reports demonstrated a 92% sensitivity and a 98% negative predictive value [7]. Importantly, the *HLA-B*1502* allele is frequent (10–15%) in populations in Hong Kong, Thailand, Malaysia and parts of the Philippines, with lower prevalence in other parts of Asia and only a 1–2% rate in Caucasians [7]. A recent study suggested that specific screening for *HLA-B*1502* may be useful and cost efficient in certain populations [7]. A potential association has been reported between the use of other aromatic anticonvulsants (phenytoin, oxcarbazepine and lamotrigine) in patients with *HLA-B*1502* and the development of Stevens–Johnson syndrome/toxic epidermal necrolysis [9,10].

Probable valid AED biomarkers

Multidrug-resistance gene 1 (for AED efficacy)

In 2003, Siddiqui *et al.* suggested an association with the 3435 CT polymorphism in the multidrug-resistance gene 1 (*MDR1*, *ABCB1*, *PGY1*) gene and resistance to AED treatment in patients with epilepsy. This study examined 200 patients with drug-resistant epilepsy, 115 patients with drug-responsive epilepsy and 200 control subjects without epilepsy [11]. The drug-resistant epilepsy group was significantly more likely to have the CC genotype at *ABCB1* 3435 than the TT genotype (odds ratio: 2.66; 95% CI: 1.32–5.38; $p = 0.006$) [11]. A review [12] of 15 subsequent association studies on *ABCB1* polymorphisms in different ethnic populations, with different AEDs and epilepsy types, as well as different definitions of drug resistance, found eight positive [11,13–19] and seven negative [20–26]. A 2008 meta-analysis of 11 case–control studies involving 1646 patients with drug-resistant epilepsy and 1725 controls found no significant association between *ABCB1* polymorphisms and AED resistance (odds ratio: 1.15; 95% CI: 0.78–1.70; $p = 0.48$) [27]. Three recent studies did not find a direct association between *ABCB1* polymorphisms and AED resistance [28–30].

CYP2C9 & *CYP2C19* (for AED metabolism & toxicity)

*CYP2C9*1* is the wild-type allele for *CYP2C9* and individuals homozygous for this allele are called extensive metabolizers [31,102]. Multiple variant alleles have been associated with significant reductions in the metabolism of *CYP2C9* substrates, compared with the *CYP2C9*1*; individuals with these genotypes are considered poor metabolizers. Similarly, *CYP2C19*1* is the wild-type allele for *CYP2C19* and individuals homozygous for this allele are called extensive metabolizers. There are multiple variants (*CYP2C19*2* to *CYP2C19*8*) that are inactive mutations responsible for the poor metabolizer phenotype [31,102].

CYP2C9/CYP2C19 & phenytoin

In humans, 80% of the drug's elimination is through 4'-hydroxylation (mediated by CYP2C9 and to a lesser extent by CYP2C19) to form 5-(4'-hydroxyphenyl)-5-phenylhydantoin (4'-HPPH) [32,33]. Nonlinear pharmacokinetics, a narrow therapeutic index and a concentration-related toxicity profile mean that small changes in CYP2C9 activity may be clinically significant for phenytoin. Multiple studies have demonstrated that subjects with variant alleles (e.g., *CYP2C9**2, *CYP2C9**3, *CYP2C9**4 and *CYP2C9**6) are phenotypically poor metabolizers of phenytoin [34–39]. These subjects have a reduced ability to metabolize phenytoin and require lower than average doses to decrease the incidence of concentration-dependent adverse effects [37,40].

As phenytoin concentration increases, the contribution of CYP2C19 to the metabolism of phenytoin increases. This suggests that CYP2C19 might be an important pathway for metabolism when CYP2C9 is saturated at phenytoin 'therapeutic concentrations' of 10–20 µg/ml (40–80 µmol/l) [41]. Approximately 1–2% of Caucasians are poor metabolizers for both CYP2C9 and CYP2C19, making them particularly susceptible to adverse effects of phenytoin [42]. In a study involving Japanese subjects, a phenytoin dose of 5 mg/kg/day resulted in predicted plasma concentrations of 18.7, 22.8 and 28.8 µg/ml, respectively, in *CYP2C19* homozygous extensive metabolizers, heterozygous extensive metabolizers and poor metabolizers [35].

CYP2C9/ABCB1 & phenytoin

A single-dose pharmacokinetic study involving 300-mg of phenytoin in 96 healthy Turkish volunteers showed the number of non-wild-type *CYP2C9* alleles explained 14.1% of the intra-patient variability in phenytoin plasma levels; the number of *ABCB1**T alleles provided some additional explanation (1.3%); and *CYP2C19**2 was not a contributory variable [43]. The combination of *CYP2C9* and *ABCB1* genotyping accounted for 15.4% of the variability in phenytoin data ($r^2 = 0.154$, $p = 0.0002$) [43]. When these results were applied to 35 patients with epilepsy being treated with phenytoin, the analysis of *CYP2C9* and *ABCB1* genotypes had "some predictive value not only in the controlled settings of a clinical trial, but also in the daily clinical practice" [43].

CYP2C9/CYP2C19 & other AEDs

No clear association exists between *CYP2C9/CYP2C19* polymorphisms and clinical response to other AEDs. Although between 20 and 30% of phenobarbital's metabolism is through CYP2C9 and CYP2C19, no conclusive relationship has been found between *CYP2C9* or *CYP2C19* genotype and either pharmacokinetics or clinical response [44–46]. CYP2C19 mediates about 33% of the *N*-demethylation of diazepam to desmethyldiazepam (nordiazepam) and 9% of the 3-hydroxylation of diazepam to temazepam at low dosages [47]. Scattered studies have noted a relationship between *CYP2C19* polymorphisms and the metabolism of diazepam and desmethyldiazepam but no clinical link [42,48].

SCN1A, SCN2A & SCN3A (for AED efficacy)

Sodium channels are composed of a large α -subunit with auxiliary β -subunits. The α -subunit is the pharmacogenetic focus because the β -subunits only modulate properties of the channel and are not required for its functioning. A 2005 study assessed whether variations in CYP2C9 and SCN1A were associated with the clinical use of carbamazepine ($n = 425$) and phenytoin ($n = 281$) [49]. The *CYP2C9**3 polymorphism was associated with the maximum dose of phenytoin ($p < 0.0066$). A functional polymorphism in the *SCN1A* gene (IVS5N+5 G>A, rs3812718) was suggested to influence the dosage requirements for the AEDs carbamazepine and phenytoin in epilepsy patients [49]. This single nucleotide

polymorphism in a 5-splice donor site was shown to influence the alternative splicing of exon 5, which codes for one of the functionally important voltage sensors of the channel [50]. The results could not be confirmed by the same researchers in a follow-up smaller study in Chinese patients despite a marginal effect noted on phenytoin pharmacodynamics [51]. A third association study was also negative [52].

One other study found an association between single nucleotide polymorphisms of SCN1A, 2A and 3A and AED responsiveness. In 471 Chinese epilepsy patients (272 drug responsive and 199 drug resistant) there was an association between SCN2A IVS7–32A>G (rs2304016) A alleles and drug resistance (odds ratio: 2.1; 95% CI: 1.2–3.7; $p = 0.007$) [53].

***HLA-A*3101* (for carbamazepine hypersensitivity reactions)**

A recent study demonstrated an association between carbamazepine-induced hypersensitivity reactions and *HLA-A*3101* in subjects of Northern European ancestry [54]. The allele occurs in 2–5% of Northern European populations and was found to be a risk factor for hypersensitivity syndrome (odds ratio: 12.41; 95% CI: 1.27–121.03), Stevens–Johnson syndrome/toxic epidermal necrolysis (odds ratio: 25.93; 95% CI: 4.93–116.18) and maculo-papular exanthema (odds ratio: 8.33, 95% CI: 3.59–19.36) [54]. The risk of these reactions increased from 5.0 to 26.0% when patients had the allele and decreased to 3.8% when the allele was absent [54].

Exploratory or research biomarkers

Some proposed exploratory biomarkers from small studies include *CYP2C9*3* (phenytoin rash) [55], GABA transporters, GABA transaminase, and the rho subunit of the GABA_c receptor (vigabatrin visual effects) [56], and serotonin transporter promoter (5-HTTLPR) and intron 2 (VNTR-2) polymorphisms (treatment response in temporal lobe epilepsy) [57].

Conclusion

To date, only *HLA-B*1502* meets the regulatory (and rigorous) definition for a known valid biomarker for AED response. The lack of other valid biomarkers does not mean none exist – on the contrary the search for epilepsy biomarkers has been primarily limited by methodological challenges. Proper study design presents a large obstacle. Ideally, pharmacogenetic association studies in epilepsy would occur in a large genetically homogenous population who were followed prospectively from onset, treated with the same medication in the same fashion, assessed using standardized objective methods for seizure freedom determination and classified by predefined definitions for treatment resistance. Most importantly, the study should have pharmacogenetic assessment as a primary or secondary outcome rather than an exploratory analysis. Ferraro *et al.* described the needed elements in more detail [58]. There are no current published pharmacogenetic studies meeting all these criteria. Without these types of studies, identification of additional valid biomarkers for AED therapy will remain serendipitous. The International League Against Epilepsy (ILAE) recent definition of drug-resistant epilepsy is a first step to standardizing how outcomes are measured and classified [59].

It may turn out that few allelic variants in any one gene have a large enough impact to alter a phenotype in an easily recognizable fashion (e.g., *HLA-B*1502*). The genetic contribution to a patient's drug response may be similar in size to all the other factors that affect that drug's pharmacokinetic and pharmacodynamic profile. If so, the best approach to identify biomarkers would be through a global pathway approach that simultaneously considers polymorphic variations in all relevant genes, proteins and metabolites. The optimal study

design and subsequent statistical approach needed to use this systems approach is not yet fully delineated but represents an exciting frontier in biomarker research.

The FDA classification approach is a useful starting framework for identifying valid biomarkers. Professional societies are starting to address the issue but no guidelines are yet published. This gap has important clinical consequences. For example, as described above, robust information exists about the role of CYP2C9 and CYP2C19 variants in phenytoin metabolism and toxicity. Phenytoin's product labelling states its "metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined" [103]. However, the FDA has not identified these variants as known valid biomarkers. Developing more clinically focused classification frameworks will probably lead to more rapid acceptance of some probable valid biomarkers (such as CYP2C9 and CYP2C19 for phenytoin) as known valid biomarkers.

In addition, the ideal classification scheme would address DNA, RNA, protein and metabolomics biomarkers. Additional studies are needed to examine the cost-effectiveness of pharmacogenetic testing and the educational needs of clinicians who must incorporate these test results into actual practice. These types of studies will help to clarify the role of advanced screening technologies, such as gene chips, in routine clinical practice.

Future perspective

The chance of identifying and confirming more 'known valid' biomarkers for AED response over the next 5–10 years depends directly on the epilepsy community's development of large multicenter collaborative research teams that prospectively implement standardized treatment strategies in homogenous new-onset epilepsy populations, evaluate outcomes using pre-determined objective measures, and implement the latest genomic, proteomic and metabolomic techniques on samples obtained prior to and during therapy. These types of studies would be expensive to properly conduct and would require significant government and private investment. Justification for this type of investment would require pharmacoeconomic evidence of potential future cost savings (for government investment) or of potential future commercialization value (for private investment). However, given the challenges and significantly larger cost of developing new medical therapies for epilepsy, it makes sense to focus more attention on the identification and validation of AED response biomarkers.

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Executive summary

- A pharmacogenetic biomarker classification based on reliability, scientific evidence and clinical relevance defines three biomarker types involved in drug response: 'known valid biomarkers', 'probable valid biomarkers' and 'exploratory or research biomarkers'.
- The only known valid antiepileptic drug biomarker is *HLA-B*1502*. This is a biomarker for the development of Stevens-Johnson syndrome in patients of specific Asian backgrounds taking carbamazepine and possibly other aromatic anticonvulsants (phenytoin, oxcarbazepine and lamotrigine).
- Probable valid antiepileptic drug biomarkers include polymorphisms in one drug transporter gene (multidrug-resistance gene 1/*MDR1/ABCB1/PGY1*), two drug metabolizing genes (*CYP2C9* and *CYP2C19*), three sodium channel genes (*SCN1A*, *SCN2A* and *SCN3A*), and one HLA allele (*HLA-A*3101*).
- The search for epilepsy biomarkers has been primarily limited by methodological challenges that can only be overcome with large-scale collaborative research efforts.