Epileptic Disord 2019; 21 (4): 330-6

Genetic literacy series: clinical application of pharmacogenetics for adverse reactions to antiepileptic drugs

An ILAE Commission Review

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Received March 30, 2018; Accepted May 18, 2019

ABSTRACT – Adverse drug reactions are a leading cause of treatment failure with antiepileptic drugs. Adverse drug reactions are also a major source of morbidity and mortality, and a substantial burden on the use and costs of health care. Recent pharmacogenetic studies have shown that some adverse drug reactions are associated with genetic variants, which has changed how we select antiepileptic drugs for individual patients. This article, beginning with a case of an adverse drug reaction induced by carbamazepine, will answer four key questions about pharmacogenetics of adverse drug reactions: (1) What types of adverse drug reactions can be caused by antiepileptic drugs? (2) What is pharmacogenetics? (3) How does pharmacogenetics play a role in the adverse drug reactions of antiepileptic drugs? and (4) How do we apply pharmacogenetic testing in clinical practice? Our goal is to increase awareness of the contributions of genetic variation to adverse drug reactions of antiepileptic drugs.

Key words: adverse drug reactions, antiepileptic drugs, pharmacogenetics

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Clinical scenario

A 14-year-old Han Chinese female with a history of focal seizures was referred to our hospital with newly diagnosed focal epilepsy. You are considering carbamazepine (CBZ) for treatment. However, you discover that her 55-year-old aunt was treated with CBZ for trigeminal neuralgia six years ago and developed Stevens-Johnson syndrome. Given this family history, what genetic tests would you consider to avoid a severe cutaneous adverse drug reaction (ADR) induced by CBZ?

doi:10.1684/epd.2019.1087

Drug therapy is the mainstay of epilepsy treatment. However, antiepileptic drugs can induce potential life-threatening ADRs as in the case mentioned above. In recent years, some pharmacogenetic studies of drug ADRs have changed how we select antiepileptic drugs for individual patients. This article will provide some information and evidence about pharmacogenetics of drug ADRs by addressing four key questions.

Q1: What types of adverse reaction can be caused by antiepileptic drugs?

Using a modified version of the WHO classification of ADRs (World Health Organization, 1972), Perucca categorized manifestations of antiepileptic drug adverse effects into five types: acute, related to the pharmacological properties of the drug (Type A, *e.g.* coordination disturbances associated with CBZ, phenytoin, benzodiazepines; cognitive dysfunction associated with benzodiazepines, topiramate); idiosyncratic reactions (Type B, *e.g.* maculopapular rashes associated with CBZ, phenytoin, phenobarbital, and lamotrigine; hepatotoxic effects associated with valproate, felbamate); chronic reactions (Type C, *e.g.* weight gain associated with valproate, gabapentin, pregabalin, vigabatrin; bilateral visual field loss induced by vigabatrin); delayed (Type D, *e.g.* impaired postnatal cognitive development associated with valproate); and secondary to drug interactions (Type E, *e.g.* decrease in serum concentrations of valproate by enzyme inducers such as CBZ, phenytoin, phenobarbital; increase in serum concentrations of phenobarbital and lamotrigine by enzyme inhibitors such as valproate) (Perucca and Gilliam, 2012). The details of descriptions and examples of each type are presented in *table 1*.

Q2: What is pharmacogenetics?

Pharmacogenetics is the study of the role of genetic variability in determining inter-individual variability in responses to pharmacological therapy (Schiavone *et al.*, 2017), which could potentially be used for treatment optimization in individual patients, resulting in a more targeted, more efficacious, and less harmful treatment (Loscher *et al.*, 2009). In general, pharmacogenetics usually refers to how variation in one single gene influences the response to a single drug. Pharmacogenomics is a broader term, which is the study of how all of the genes (the genome) can influence responses to drugs. The inter-individual variations in drug response, including drug efficacy and toxicity, are multifactorial and multiple genes have been identified including genes that encode metabolising enzymes, drug transporters, drug targets, and genes with immune function such as HLA. In this article, we focus primarily on the role of genetic variability in influencing ADRs to antiepileptic drugs.

Q3: How does pharmacogenetics play a role in ADRs to antiepileptic drugs?

Association with HLA-B*1502/HLA-A*3101 and CBZ-induced SJS/TEN

The mechanism of genetic variability on the ADRs of antiepileptic drugs is not fully understood. Some investigations on genes that control immune-mediated hypersensitivity reactions, namely type B effects (*table 1*), have shown important results that are relevant to clinical practice. Amongst these studies, the most convincing evidence is of the association between human leukocyte antigen HLA-B*1502 and CBZ-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The prevalence of specific HLA alleles differs significantly between ethnic groups. Based on the Allele Frequency Net database (http://www.allelefrequencies.net/hla-adr/default.asp), we identified that the prevalence of HLA-B*1502 allele in Asian populations (allele frequency in Han Chinese: 12.87%; in Singapore: 11.6%; in Malay: 12.25%; in Vietnam: 13.5%) was much higher than in Caucasian (allele frequency<0.1%) and African populations (allele frequency<2%). Most of the studies of association between HLA-B*1502 allele and SJS/TEN were reported in Asian groups. The first study reporting an association between HLA-B*1502 allele and SJS/TEN in Han Chinese populations was reported by Chung *et al.* (2004). These authors genotyped 44 Han Chinese patients with CBZ-induced SJS, 101 CBZ-tolerant patients, and 93 healthy controls without a history of CBZ use. HLA-B*1502 allele was present in all CBZ-induced SJS patients but in only 3% of CBZ-tolerant patients (OR=2504; 95% CI: 126-49522) and in 9% of the control population (OR=895; 95% CI: 50-15869). Since then, the association has been replicated several times in the Chinese population (Man *et al.*, 2007; Wang *et al.*, 2011; Zhang *et al.*, 2011; Shi *et al.*, 2012), and has also been found in individuals of Thai (OR=75.4, 95% CI=13.0-718.9), Malaysian, and Indian (OR=71.40; 95% CI: 3.0-1698) ethnicity (Mehta *et al.*, 2009; Then *et al.*, 2011; Kulkantrakorn *et al.*, 2012). HLA-B*1502 may also be associated with severe cutaneous reactions induced by lamotrigine or phenytoin (Man *et al.*, 2007; Cheung *et al.*, 2013). Moreover, the role of ethnicity is emphasized by data confirming the association between CBZ-induced SJS/TEN and the HLA-B*1502 allele in Asians, but not in Caucasians (Lonjou *et al.*, 2006). The association between HLA-B*1502 allele and SJS/TEN displayed interethnic differences in the

Table 1. Adverse effects of antiepileptic drugs based on a modified version of the WHO classification (World Health Organization, 1972).

Type	Description	Examples
A	Related to the known mechanism of action of the drug; common (1-10%) or very common (>10%); acute; dependent on dose or serum concentration; predictable; reversible	Drowsiness, lethargy, tiredness, fatigue, insomnia Dizziness, unsteadiness, vertigo, imbalance, ataxia, diplopia, tremor Cognitive impairment Irritability, aggressive behaviour, depression; gastrointestinal symptoms Hyponatraemia Paraesthesia
B	Related to individual vulnerability (immunological, genetic, or other mechanism); uncommon (0·1-1%) or rare (<0·1%); develop during the first few weeks of treatment; unpredictable; high morbidity and mortality; reversible	Skin rashes, severe mucocutaneous reactions (drug rash with eosinophilia and systemic symptoms, toxic epidermal necrolysis, Stevens-Johnson syndrome) Aplastic anaemia, agranulocytosis Hepatotoxic effects, pancreatitis Angle closure glaucoma Aseptic meningitis
C	Related to the cumulative dose of the drug; common (1-10%); chronic; mostly reversible	Decreased bone mineral density Weight gain, weight loss Folate deficiency Connective tissue disorders Hirsutism, gingival hypertrophy Alopecia Visual field loss
D	Related to prenatal exposure to the drug *(e.g.* teratogenesis) or carcinogenesis; uncommon (0·1-1%); delayed; dose dependent; irreversible	Birth defects Neurodevelopmental delay in the offspring Pseudolymphoma
E	Adverse drug interactions; common (1-10%); predictable; reversible	Increased risk of skin rash after adding lamotrigine to valproate Reduced seizure control after adding the combined contraceptive pill to lamotrigine Reduced effectiveness of warfarin after adding carbamazepine Increased risk for CNS neurotoxicity after combination of sodium channel-blocking antiepileptic drugs

prevalence of HLA-B*1502, which might account for a higher incidence of CBZ-induced SJS in Asians compared with Caucasians.

Among other HLA genotypes that predispose to antiepileptic-induced adverse reactions, three studies have also reported an association between HLA-A*3101 and CBZ-induced SJS/TEN and hypersensitivity syndrome in Japanese (OR=10.8; 95% CI: 5.9-19.6), North European (OR=25.9; 95% CI: 4.9-116.1), and Korean (OR=12.4; 95% CI: 4.5-34.1) patients (Kim *et al.*, 2011; McCormack *et al.*, 2011; Ozeki *et al.*, 2011). Information on HLA allele associations and antiepileptic drugs can be found in the Allele Frequency Net database- ADR section.

Other associations between genetic variants and AED adverse effects

In addition to immune-mediated hypersensitivity reactions induced by CBZ, other types of adverse effects associated with genetic variants are noteworthy. For example, *CYP2C9* polymorphisms are an important determinant of the rate of phenytoin metabolism. Individuals carrying *CYP2C9* alleles that encode variant enzymes with reduced activity to metabolise phenytoin, at a considerably slower rate compared with individuals homozygous for the wild-type allele (CYP2C9*1), therefore have a greater risk of developing concentration-dependent

neurotoxicity (Type A) (Lee *et al*., 2002; Depondt *et al*., 2011) (*table 1*). In 2018, McCormack *et al*. found that a rare variant in the complement factor H-related 4 (*CFHR4*) gene was associated with an increased risk of phenytoin-induced maculopapular exanthema (MPE) in Europeans (OR=7; 95% CI: 3.2-16). The identified variant (c.59-2448T>G) tags a missense variant (Asn1050Tyr) in the complement factor H (CFH) gene, suggesting that aberrant complement activation plays a role in phenytoin hypersensitivity (McCormack *et al*., 2018). In addition, valproate increases the risk of neural tube defects, and a number of studies have shown that there is a subset of women with epilepsy taking valproate who have had repeated pregnancies with neural tube defects despite folate supplementation (Omtzigt *et al*., 1992; Duncan *et al*., 2001). These women have been suggested to be more susceptible to the effects of valproate, because the drug upregulates the expression of the key enzyme in folate interconversion, 5′-10′-methylenetetrahydrofolate reductase (MTHFR) (Christensen *et al*., 1999). Interestingly, there is evidence that polymorphism in the *MTHFR* gene (c.677C>T, p.Ala222Val) is a risk factor for neural tube defects (Christensen *et al*., 1999). In two relatively small studies, each involving fewer than 200 mother-child pairs, a non-significant trend was identified towards a maternal 677TT genotype and an increased risk for neural tube defects following exposure to AEDs *in utero*, but no associations were found between the children's *MTHFR* genotype and major malformations (Kini *et al*., 2007; Dean *et al*., 2007). These studies show that this *MTHFR* genotype has no major effect on susceptibility to AED teratogenicity, although a modest effect cannot be excluded. The aetiological basis of neural tube defects remains poorly understood, thus other factors, including genetic and environmental factors, may also be contributory.

Another example is valproate-induced hepatotoxicity (Type B) (*table 1*). An association between variants in *POLG* and valproate-induced hepatotoxicity was found based on a multicentre study (Stewart *et al*., 2010). Further studies are needed regarding risk stratification and economic analyses before *POLG* testing can be recommended prior to instituting valproate therapy to reduce the risk of this rare but severe idiosyncratic adverse event. On the other hand, sequencing of *POLG* is warranted if severe hepatotoxicity occurs after taking valproate routinely.

Q4: How do we apply pharmacogenetic testing in clinical practice?

As mentioned above, the fact that dangerous or even fatal skin reactions (SJS and TEN) to CBZ are significantly more common in Asian patients with HLA-B*1502 or HLA-A*3101 has important implications for clinical practice. Patients with ancestry from areas in which HLA-B*1502 or HLA-A*3101 are present should thus be screened for the HLA-B*1502 or HLA-A*3101 allele before starting treatment with CBZ. In 2007, the US Food and Drug Administration (FDA) issued an alert recommending screening for HLA-B*1502 before commencing CBZ. They also recommended that CBZ should not be started if the patient tests positive for HLA-B*1502 unless the expected benefit clearly outweighs the increased risk of serious skin reactions (US Food and Drug Administration website). This key FDA recommendation made screening for the HLA-B*1502 allele the first clinical test of epilepsy pharmacogenetics to be used in routine clinical practice. In 2014, Amstutz *et al*. published recommendations for HLA-B*1502 and HLA-A*3101 genetic testing, which suggested that genetic testing for HLA-B*1502 and HLA-A*3101 were recommended for all CBZ-naïve patients before initiation of CBZ therapy (Amstutz *et al*., 2014).

Does genotyping prevent CBZ-induced SJS/TEN? In a study of 4,855 Taiwanese Han Chinese patients, prospective genotyping of HLA-B*1502 was performed as screening before initiation of CBZ therapy (Chen *et al*., 2011). Those testing positive for HLA-B*1502 (372 patients; 7.7%) were advised not to take CBZ and were given an alternative medication, or advised to continue taking their pre-study medication; those testing negative (4,483 patients; 92.3%) were allowed to take CBZ (Chen *et al*., 2011). The results showed that SJS-TEN did not develop in any of the HLA-B*1502-negative subjects receiving CBZ. Compared to the historical incidence of SJS/TEN in the same Taiwanese population, it was estimated that 10 CBZ-SJS/TEN cases were prevented with HLA-B*1502 screening (Chen *et al*., 2011). These results suggest that genotyping for the HLA-B*1502 allele and avoidance of CBZ therapy in these HLA-B*1502-positive subjects was strongly associated with a significant decrease in the incidence of CBZ-induced SJS/TEN. Based on the population frequency data available for HLA-B*1502 and HLA-A*3101, genetic testing for HLA-B*1502 and HLA-A*3101 were beneficial in patients of all ancestries, especially originating from a population where HLA-B*1502 and HLA-A*3101 are common (*e.g*. Chinese, Thai, Indian, Malay, Filipino, Indonesian populations) (Amstutz *et al*., 2014).

Who should receive clinical pharmacogenetic testing?

– In antiepileptic drug-naïve epilepsy patients for whom CBZ is being considered, the managing physician should screen for HLA-B*1502 and HLA-A*3101 before antiepileptic drug therapy if the patient belongs to an ethnic group in which HLA-B*1502 and HLA-A*3101 are found.

– In patients who have previously taken CBZ for a duration of ≤three months, there is the possibility of ADRs occurring even if no symptoms were

observed during the previous administration, due to their delayed onset, and genetic testing should be considered in such patients. However, in patients who have been taking CBZ for >three months without developing skin reactions, it is unnecessary to genotype for HLA-B*1502 or HLA-A*3101 as they have declared themselves to be at low risk of SJS/TEN from CBZ (US Food and Drug Administration website).

– In patients who have previously experienced hypersensitivity reactions (HSRs) potentially related to CBZ, genetic testing is recommended as part of the differential diagnosis and for the direction of future therapy. If the genetic test for HLA-B*1502 or HLA-A*3101 is positive, alternative medications should be used as first-line therapy. Consideration in the choice of alternative medications should be given to the possibility of cross-reactivity with structurally similar AEDs (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, and primidone). Phenytoin, CBZ and lamotrigine block neuronal voltage-gated Na^+ channels and share a common binding site to domain IV-S6 in the channel's inner pore. (Kuo, 1998) Because of their structural similarity to CBZ, patients who are at increased risk of CBZ hypersensitivity may also have an increased risk for developing HSRs. Associations between HLA-B*1502 and SJS/TEN have been reported for phenytoin and lamotrigine. However, the strength of the reported associations was moderate, with only 8/26 (31%) patients with phenytoin-induced SJS/TEN (Hung *et al*., 2010) and 5/19 (26%) patients with lamotrigine-induced SJS/TEN (Hung *et al*., 2010; Shi *et al*., 2011) carrying HLA-B*1502. Current evidence therefore suggests an increased risk of SJS/TEN for patients who are positive for HLA-B*1502 when taking phenytoin or lamotrigine, however, the associated risk appears to be lower than that for CBZ (Amstutz *et al*., 2014). The first choice should be given to alternative medications that are structurally different from CBZ. If structurally different medications are not effective or not tolerated, aromatic AEDs other than CBZ or OXC should be used. If the patient tests negative, he/she is at low risk of CBZ-induced SJS/TEN, and the physician can prescribe CBZ with appropriate counselling. However, even with negative test results, patients should be made aware of the symptoms of severe CBZ HSRs, in order to enable rapid discontinuation of the drug if HSR occurs.

Cost-effectiveness analysis is also important for clinical implementation of pharmacogenetics testing, and may provide policy makers with the necessary evidence to promote more rapid and extensive adoption. Cost effectiveness of pharmacogenetics testing is sensitive to the prevalence of genotypes in a population. HLA-B*1502 is particularly prevalent in East Asian and Southeast Asia. Based on a previous study, genotyping prior to the use of CBZ was shown to be cost-effective for Chinese and Malay people, but not for Indians in Singapore (Dong *et al*., 2012). Genetic testing for HLA-B*1502 has been routine in Taiwan, with the genotyping fee covered by national health insurance. In contrast, Chen *et al*. found that HLA-B*1502 testing, as implemented in Hong Kong, was not cost-effective (Chen *et al*., 2016), however, a wide range of assumptions may be made regarding the economic modelling, leading to a number of possible significant biases that make it difficult to assess whether the policy of HLA-B*15:02 was the main factor responsible for the changes observed. In terms of HLA-A*3101, a UK study found that genotyping prior to prescribing CBZ was cost-effective for patients with newly diagnosed epilepsy (Plumpton *et al*., 2015).

Scenario resolution

*The patient was screened for the HLA-B*1502 allele. The test was positive; levetiracetam was thus prescribed. The managing physicians deliberately avoided carbamazepine, oxcarbazepine, lamotrigine, phenytoin and phenobarbital given that the expected benefit clearly outweighed the increased risk of severe skin reactions. The patient's family members were also advised to undergo HLA-B*1502 screening if they needed to use the aromatic antiepileptic drugs in the future.*

There is an increasing awareness of the contributions of genetic variation in ADRs of antiepileptic drugs. Although HLA-B*1502 screening has successfully reduced the incidence of CBZ-induced SJS/TEN, we are still appraising the clinical usefulness of other pharmacogenetic tests in epilepsy. However, there is no doubt that more evidence-based pharmacogenetic testing will emerge in the near future, which augurs well for clinical practice. □

Key points

- Inter-individual variations in drug adverse drug reactions may be due to genetic factors.
- The HLA-B*1502 allele is associated with carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis; this allele is present in people of Asian ancestry but rare in Caucasians.
- When considering carbamazepine use in patients of Asian ancestry, screening for the HLA-B*1502 allele should be done before commencing usage.
- Screening has been shown to reduce the incidence of carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis.

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Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.
This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

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TEST YOURSELF

(1) A 15-year-old patient is diagnosed with focal epilepsy. Both his parents are Han Chinese. You are considering treating him with an antiepileptic drug. Which of your antiepileptic drug choices would prompt you to do screening for HLA-B*1502 before commencing drug treatment?

A. levetiracetam
B. valproic acid
C. topiramate
D. carbamazepine

(2) You are planning to start antiepileptic drug treatment for a 30-year-old female with focal epilepsy. Her HLA-B*1502 test comes back as positive for the HLA-B*1502 allele. Which of the following antiepileptic drugs can be used safely, given the positive test?

A. carbamazepine
B. lamotrigine
C. levetiracetam
D. phenytoin

Also available at http://www.geneticliteracy.info/gl-test6

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".