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Phenytoin Therapy and *HLA-B*15:02* and *CYP2C9* Genotypes

Laura Dean, MD[1]

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Introduction

Phenytoin is an antiseizure medication used for the prevention of focal seizures and generalized tonic-clonic convulsions (1).

Phenytoin has a narrow therapeutic index—patients that have toxic blood concentrations of phenytoin have inreased risks of acute side effects. Dosing can be complex due to pharmacokinetic factors, including patient weight, age, sex, concomitant medications, plasma binding protein stats, the presence of uremia or hyperbilirubinemia, and specific pharmacogenetic variants. As such, therapeutic drug monitoring is often used to adjust dose and maintain serum concentrations within the therapeutic range (10–20 µg/mL).

CYP2C9 is one of the main enzymes involved in the metabolism of phenytoin, and variant *CYP2C9* alleles are known to influence phenytoin drug levels. Individuals who carry decreased activity *CYP2C9* variants may have reduced clearance rates of phenytoin and be at greater risk for dose-related side effects (2).

An individual's human leukocyte antigen B (*HLA-B*) genotype is a known risk factor for drug-induced hypersensitivity reactions. HLA-B has an important immunological role in pathogen recognition and response, as well as to non-pathogens such as drugs. Carriers of the variant *HLA-B*15:02* allele are at high risk of developing potentially life-threatening phenytoin-induced Stevens-Johnson syndrome (SJS) and the related toxic epidermal necrolysis (TEN).

The *HLA-B*15:02* variant is most commonly found among individuals of Southeast Asian descent, where there is a strong association between SJS/TEN and exposure to carbamazepine. Carbamazepine is an antiseizure medication used to treat the same types of seizures as phenytoin, as well as trigeminal neuralgia and bipolar disorder.

The FDA-approved drug label for phenytoin states that consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*15:02*. The label also mentions that variant *CYP2C9* alleles may contribute to unusually high levels of phenytoin (1).

The Clinical Pharmacogenetics Implementation Consortium (CPIC) recommends the use of an antiseizure medication other than carbamazepine, phenytoin (or its prodrug fosphenytoin) for any *HLA-B*15:02* carrier regardless of *CYP2C9* genotype, patient ancestry or age. CPIC also recommends consideration of at least a 25% reduction in the starting maintenance dose for patients who are *CYP2C9* intermediate metabolizers and *HLA-B*15:02* negative, and at least a 50% reduction for *CYP2C9* poor metabolizers and *HLA-B*15:02* negative, with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response (Table 1) (2).

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Table 1. 2014 Therapeutic recommendations for phenytoin therapy based on *HLA-B* and *CYP2C9* genotypes, adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC)

Phenotype	*HLA-B*15:02* positive		*HLA-B*15:02* negative	
	Implication	Therapeutic recommendation	Implication	Therapeutic recommendation
CYP2C9 normal metabolizer	Increased risk of phenytoin- induced SJS/ TEN	If patient is phenytoin naive,[A] do not use phenytoin/ fosphenytoin[B]	Normal phenytoin metabolism	Initiate therapy with recommended maintenance dose [C]
CYP2C9 intermediate metabolizer	Increased risk of phenytoin- induced SJS/ TEN	If patient is phenytoin naive,[A] do not use phenytoin/ fosphenytoin[B]	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 25% reduction of recommended starting maintenance dose.[C] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response
CYP2C9 poor metabolizer	Increased risk of phenytoin- induced SJS/ TEN	If patient is phenytoin naive,[A] do not use phenytoin/ fosphenytoin[B]	Reduced phenytoin metabolism. Higher plasma concentrations will increase probability of toxicities	Consider 50% reduction of recommended starting maintenance dose.[C] Subsequent maintenance doses should be adjusted according to therapeutic drug monitoring and response

SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis.
The strength of the therapeutic recommendations is classified as "strong" for all recommendations, with the exception of the recommendation for *CYP2C9* intermediate metabolizers who are *HLA-B*15:02* non carriers, which is classified as "moderate".
[A] If the patient has previously used phenytoin for longer than 3 months without incidence of cutaneous adverse reactions, reinitiate phenytoin with caution. Adjust dose based on *CYP2C9* genotype if known.
[B] Carbamazepine should not be used as an alternative. Alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine have some evidence linking SJS/TEN with the *HLA-B*15:02* allele, and thus caution should be used in choosing alternatives to phenytoin).
[C] Recommended maintenance dose based on patient's clinical characteristics.
Table is adapted from Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clinical pharmacology and therapeutics. 2014:96(5):542-8 (2).
Note: The nomenclature used in this table reflects the standardized pharmacogenetic terms proposed by CPIC (3).

Drug: Phenytoin

Phenytoin is a generic antiseizure drug that is rarely prescribed to newly diagnosed patients due to its propensity for long-term side effects. Nevertheless, it continues to be used by many patients who initiated treatment prior to the availability of newer medications that have fewer side effects and drug-drug interactions. Phenytoin is used for the control of partial seizures and generalized tonic-clonic convulsions. It is also used in the treatment of status epilepticus and may be used to prevent or treat seizures that occur during and following neurosurgery (1).

Phenytoin belongs to the sodium channel blockers class of antiseizure drugs, which are thought to suppress seizure activity by blocking voltage-gated sodium channels that are responsible for the upstroke of action potentials (4, 5). The block by phenytoin and other members of this class of antiseizure drugs occurs in a state-dependent fashion, with preferential binding and block of the inactivated state of the channel. This results in voltage- and frequency-dependent block in which high frequency action potential firing, which occurs during epileptic activity, is preferentially inhibited (1, 6)

The dosing of phenytoin can be complex, as treatment is typically initiated at a low starting dose, which considers patient age, weight, and the presence of concomitant medications that may influence phenytoin metabolism or protein binding. The dose is then carefully escalated to obtain the desired therapeutic effect. There is a wide variation in how individuals respond to phenytoin (2). Therapeutic drug monitoring is often used to adjust the dose to ensure that plasma levels are within therapeutic range (10–20 µg/dl in adults). Measurement of plasma levels is useful when adding or discontinuing concomitant medications that effect phenytoin levels. Periodic measurement of plasma phenytoin concentrations may also be valuable in pregnancy, because altered phenytoin pharmokinetics increases the risk of seizures.

Phenytoin use during pregnancy has been associated with an 11% risk in the offspring of the fetal hydantoin syndrome, in which there is dysmorphism, hypoplasia and irregular ossification of the distal phalanges. Facial dysmorphism includes epicanthal folds, hypertelorism, broad flat nasal bridges, an upturned nasal tip, wide prominent lips, and, in addition, distal digital hypoplasia, intrauterine growth retardation, and mental retardation. An additional 30% of the *in utero*-exposed children express fetal hydantoin effects, in which there is a more limited pattern of dysmorphic characteristics. Some studies have found significant associations between in utero exposure to phenytoin and major congenital abnormalities (mainly, cardiac malformations and cleft palate) whereas others have failed to find such associations (7, 8).

The adverse effects of phenytoin fall into two categories, types A and B. Type A adverse drug reactions account for up to 90% of reactions. They are predictable and can occur in any individual if their drug exposure is high enough. Some of these reactions occur rapidly and are reversible when the dose is reduced. These include acute central nervous system adverse effects such as sedation, nystagmus, and ataxia. Other common side effects occur with long-term exposure and include changes to the physical appearance, such as gingival hyperplasia, coarsening of the facial features, hirsuitism, and acne.

Type B adverse drug reactions include idiosyncratic hypersensitivity reactions. Such reactions can occur at any dose and develop through a mechanism that is unrelated to the mechanism of action of the drug.

A rare but life-threatening hypersensitivity reaction associated with phenytoin treatment is Stevens-Johnson syndrome (SJS) and the related toxic epidermal necrolysis (TEN). Both are severe cutaneous reactions to specific drugs, and are characterized by fever and lesions of the skin and mucous membranes, with a mortality rate of up to 30% (9).

It is difficult to predict in whom a drug-induced hypersensitivity reaction is likely to occur. For phenytoin, however, carriers of a specific *HLA* variant are known to be susceptible to phenytoin-induced SJS/TEN. *HLA* testing of patients can identify those at-risk individuals so that an alternative drug can be used.

HLA gene family

The human leukocyte antigen (*HLA*) genes are members of the Major Histocompatability Complex (*MHC)* gene family, which includes more than 200 genes. The *MHC* family has been subdivided into three subgroups based on the structure and function of the encoded proteins: Class I, Class II, and Class III. The class I region contains the genes encoding the HLA molecules HLA-A, HLA-B, and HLA-C. These molecules are expressed on the surfaces of almost all cells and play an important role in processing and presenting antigens. The class I gene region also contains a variety of other genes, many of which are not known to be involved in immune function.

An important role of HLA class I molecules is to present peptide fragments to immune cells (CD8+ T cells). Most of these peptides originate from the breakdown of normal cellular proteins (“self”). However, if foreign peptide fragments are presented, e.g., from a pathogen, CD8+T cells will recognize the peptides as “non-self” and will be activated to release inflammatory cytokines and launch an immune response to dispose of the pathogen (or foreign body).

Because HLA molecules need to present such a wide variety of "self" and "non-self" peptides, the HLA genes are both numerous and highly polymorphic. More than 1,500 HLA-B alleles have been identified (10). HLA allele nomenclature includes the HLA prefix, followed by the gene, an asterisk and a two digit number that corresponds to antigen specificity, and the assigned allele number (11). For example, the *HLA-B*15:02* allele is composed of:

- HLA: the HLA prefix (the HLA region on chromosome 6)
- B: the B gene (a particular HLA gene in this region)
- 15: the allele group (historically determined by serotyping, i.e., a group of alleles that share the same serotype)
- 02: the specific HLA allele (a specific protein sequence; determined by genetic analysis).

Additional digits have recently been added to the nomenclature to discriminate alleles that do not differ in the protein amino acid sequence, but differ in their genetic sequence (i.e., due to synonymous and noncoding genetic variants).

Variation in *HLA* genes plays an important role in the susceptibility to autoimmune disease and infections and they are also critical in the context of transplant surgery where better outcomes are observed if the donor and recipient are HLA-compatible.

More recently, *HLA* variants have been associated with susceptibility to Type B adverse drug reactions. For example, *HLA-B* variants have been associated with severe hypersensitivity reactions to abacavir (used to treat HIV), allopurinol (used to treat gout), and the antiepileptic drugs, carbamazepine and phenytoin.

Gene: *HLA-B*15:02*

Individuals who carry one or two copies of the high risk *HLA-B*15:02* allele are known as *HLA-B*15:02* positive (Table 2).

Table 2. 2014 Assignment of likely HLA-B phenotype based on genotype (CPIC)

Likely phenotype[a]	Genotype	Examples of diplotypes
Negative High-risk *HLA-B*15:02* allele not detected (constitutes ~98.6% of patients)	No copies of high-risk *HLA-B*15:02* allele	*X/*X[b]
Positive Detection of high-risk *HLA-B*15:02* allele (constitutes ~1.4% of patients)	Homozygous or heterozygous for high-risk *HLA-B*15:02* allele	*15:02/*X[b], *15:02/*15:02

[a] Global frequencies presented in parentheses. Haplotype frequencies vary among populations; please see (2) for individual population frequencies

[b] Where *X = any genotype other than *15:02.

Table is adapted from Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clinical pharmacology and therapeutics. 2014:96(5):542-8 (2).

Note: The nomenclature used in this table reflect the standardized pharmacogenetic terms proposed by CPIC (3).

The association between the *HLA-B*15:02* allele and SJS/TEN was first reported with the use of carbamazepine in the Han Chinese population. In the initial study, all patients who had carbamazepine-induced SJS/TEN were found to be a carrier of the *HLA-B*15:02* allele (44/44, 100%), whereas the allele was much less common among carbamazepine-tolerant patients (3/101, 3%)(12). In subsequent studies, this association was replicated, with a *HLA-B*15:02* carrier frequency of 70100% among cases of carbamazepine-induced SJS/TEN (13).

The *HLA-B*15:02* allele was later associated with phenytoin-induced hypersensitivity reactions, including phenytoin-induced SJS in a Thai population and phenytoin-induced SJS/TEN in Chinese Asians (14, 15).

There are fewer studies on phenytoin-induced hypersensitivity then carbamazepine, and the strength of association between phenytoin and SJS/TEN is weaker than that of carbamazepine and SJS/TEN. However, from the evidence available, the FDA recommends consideration of avoiding phenytoin as an alternative treatment to carbamazepine in individuals who are carriers of *HLA-B*15:02* (2).

The prevalence of carbamazepine-induced SJS/TEN is higher in populations where *HLA-B*15:02* is more common. Of note, the *HLA-B*15:02* allele frequency is highest in Southeast Asia, as populations from Hong Kong, Thailand, Malaysia, Vietnam, and parts of the Philippines have an allele frequency > 15%. It is slightly lower (~ 10-13%) in Taiwan and Singapore, and around 4% in North China. South Asians, including Indians, appear to have a *HLA-B*15:02* allele frequency of ~2 to 4%, with higher frequencies in some subpopulations (12-14, 16-27).

The *HLA-B*15:02* allele is rare (< 1%) in East Asia (Japan and Korea) and among individuals who are not of Asian descent. For example, the variant is very rare in Europeans, Hispanics, Africans, African Americans, and Native Americans (13, 18).

Gene: *CYP2C9*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs in the liver. The CYP450 genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

The *CYP2C9* gene is highly polymorphic, with more than 50 known alleles. Variation in *CYP2C9* is thought to contribute to the pharmacogenetic variability in phenytoin metabolism.

*CYP2C9*1* is the wild-type allele and is associated with normal enzyme activity (2). Individuals who have two normal-function alleles (e.g., *CYP2C9 *1/*1*) are classified as "normal metabolizers" (Table 3). For individuals who are CYP2C9 normal metabolizers, the recommended starting maintenance dose of phenytoin does not need to be adjusted based on genotype (2).

Table 3. 2014 Assignment of likely *CYP2C9* phenotype based on genotype (CPIC)

Likely phenotype[a]	Genotype	Examples of diplotypes
Normal metabolizer (normal activity) (constitutes ~91% of patients)	An individual carrying two normal-function alleles	**1/*1*
Intermediate metabolizer (heterozygote or intermediate activity) (constitutes ~8% of patients)[b]	An individual carrying one normal-function allele plus one decreased-function allele	**1/*3, *1/*2*
Poor metabolizer (homozygous variant, low or deficient activity) (constitutes ~1% of patients)	An individual carrying two decreased function alleles	**2/*2, *3/*3, *2/*3*

[a] Global frequencies presented in parentheses. Haplotype frequencies vary among populations; please see (2) for individual population frequencies

[b] The enzyme activity in this grouping varies widely. Please see (2) for activity ranges.

Table is adapted from Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MT, Klein TE, Callaghan JT. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clinical pharmacology and therapeutics. 2014:96(5):542-8 (2).

Note: The nomenclature used in this table reflect the standardized pharmacogenetic terms proposed by CPIC (3).

Two allelic variants associated with reduced enzyme activity are *CYP2C9*2* and **3*. The **2* allele is more common in Caucasian (10-20%) than Asian (1-3%) or African (0-6%) populations, whereas the **3* allele is less common (<10% in most populations) and is extremely rare in African populations (24, 25, 28-30).

Individuals with one decreased function allele (e.g., *CYP2C9*1/*2* and **1/*3*) have mild to moderately reduced clearance of phenytoin; these individuals are classified as CYP2C9 intermediate metabolizers. The CPIC recommendations for CYP2C9 intermediate metabolizers include "to consider at least a 25% reduction of the recommended starting maintenance dose" (2).

Individuals with two decreased function alleles (e.g., *CYP2C9*2/*2*, **3/*3*) have reduced clearance of phenytoin and are classified as CYP2C9 poor metabolizers. CPIC recommendations for CYP2C9 poor metabolizers include "to consider at least a 50% reduction of the starting maintenance dose" (2).

In African Americans, the *CYP2C9*5*, **6*, **8* and **11* variants are more common, and these variants are also associated with a decrease in phenytoin metabolism (31).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests that are currently available for the phenytoin drug response, the HLA-B gene, and the CYP2C9 gene.

The genotype results for an *HLA* allele such as *HLA-B*15:02* can either be "positive" or "negative." There are no intermediate phenotypes because the HLA genes are expressed in a codominant manner.

A positive result indicates the individual is either "heterozygous" or "homozygous" for the variant, depending upon whether they are carrying one or two copies of the **15:02* allele, respectively.

A negative result indicates that the individual does not carry the *HLA-B*15:02* allele. However, a negative result does not rule out the possibility of a patient developing phenytoin-induced SJS/TEN. Therefore, clinicians should carefully monitor all patients according to standard practices.

For *CYP2C9*, the variants that are routinely tested for include *CYP2C9*2* and **3*. Results are typically reported as a diplotype, such as *CYP2C9 *1/*2*.

Therapeutic Recommendations based on Genotype

This section contains excerpted[1, 2] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

2015 Statement from the US Food and Drug Administration (FDA)

Regarding HLA-B:

Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of *HLA-B*1502*, an inherited allelic variant of the *HLA B* gene, in patients using carbamazepine. Limited evidence suggests that *HLA-B*1502* may be a risk factor for the development of SJS/TEN in patients of Asian ancestry taking other antiepileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for *HLA-B*1502*.

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labeled all formulations containing the generic drug.

[2] Square brackets indicate insertions by the author to reflect the standardized nomenclature for pharmacokinetic terms proposed by CPIC in 2016 3. Caudle, K.E., H.M. Dunnenberger, R.R. Freimuth, J.F. Peterson, et al., Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med, 2016.

The use of *HLA-B*1502* genotyping has important limitations and must never substitute for appropriate clinical vigilance and patient management. The role of other possible factors in the development of, and morbidity from, SJS/TEN, such as antiepileptic drug (AED) dose, compliance, concomitant medications, comorbidities, and the level of dermatologic monitoring have not been studied.

Regarding CYP2C9:

In most patients maintained at a steady dosage, stable phenytoin serum levels are achieved. There may be wide interpatient variability in phenytoin serum levels with equivalent dosages. Patients with unusually low levels may be noncompliant or hypermetabolizers of phenytoin. Unusually high levels result from liver disease, variant *CYP2C9* and *CYP2C19* alleles, or drug interactions which result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful. As phenytoin is highly protein bound, free phenytoin levels may be altered in patients whose protein binding characteristics differ from normal.

Please review the complete therapeutic recommendations that are located here: (1).

2014 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

Regarding HLA-B: […] Therefore, regardless of the *CYP2C9* genotype and the individual's ancestry or age, if the *HLA-B*15:02* test result is positive, the recommendation is to consider using an anticonvulsant other than carbamazepine and phenytoin, unless the benefits of treating the underlying disease clearly outweigh the risks. Some evidence exists linking SJS/TEN with the *HLA-B*15:02* allele in association with the use of alternative medications such as oxcarbazepine, eslicarbazepine acetate, and lamotrigine, and thus caution should be used in choosing alternatives to phenytoin.

Regarding CYP2C9: The recommended phenytoin maintenance dose does not need adjustment based on genotype for CYP2C9 extensive ["normal"] metabolizers. Available evidence does not clearly indicate the amount of dose reduction needed to prevent phenytoin-related toxicities in CYP2C9 intermediate and poor metabolizers; thus, our recommendations should be considered conservative estimates, given the variability surrounding phenytoin dosing in an individual. On the basis of the doses reported in the pharmacokinetic and pharmacogenetic studies mentioned above and in Supplementary Table S9 online, at least a 25% reduction of the recommended starting maintenance dose may be considered for CYP2C9 intermediate metabolizers, with subsequent maintenance doses adjusted based on therapeutic drug monitoring and response. For CYP2C9 poor metabolizers, consider at least a 50% reduction of starting maintenance dose, with subsequent maintenance doses adjusted based on therapeutic drug monitoring or response.

Please review the complete therapeutic recommendations that are located here: (2).

Nomenclature of selected *HLA-B* alleles

Allele name	dbSNP reference identifier for allele location
*HLA-B*15:02*	rs2844682 and rs3909184

For the *MHC* region, variations in genes such as *HLA-B* occur across the whole sequence of the gene, not a single locus. Therefore, the *HLA-B*15:02* allele is defined by its sequence rather than single coding or protein variations. If there is strong linkage disequilibrium between one or more SNPs and a specific *HLA* allele, the presence of these SNPs (tag SNPs) may be used for *HLA* typing in some populations; however, genotyping tag SNPs should not be considered diagnostic or equivalent to actual HLA testing. For *HLA-B*15:02*, rs2844682 and rs3909184 are the tag SNPs (32).
Guidelines on nomenclature of the HLA system are available from HLA Nomenclature: http://hla.alleles.org/

Nomenclature of selected *CYP2C9* alleles

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2C9*2*	430C>T Arg144Cys	NM_000771.3:c.430C>T	NP_000762.2:p.Arg144Cys	rs1799853
*CYP2C9*3*	1075A>C Ile359Leu	NM_000771.3:c.1075A>C	NP_000762.2:p.Ile359Leu	rs1057910
*CYP2C9*5*	1080C>G Asp360Glu	NM_000771.3:c.1080C>G	NP_000762.2:p.Asp360Glu	rs28371686
*CYP2C9*6*	817delA Lys273Argfs	NM_000771.3:c.817delA	NP_000762.2:p.Lys273Argfs	rs9332131
*CYP2C9*8*	449G>A Arg150His	NM_000771.3:c.449G>A	NP_000762.2:p.Arg150His	rs7900194
*CYP2C9*11*	1003C>T Arg335Trp	NM_000771.3:c.1003C>T	NP_000762.2:p.Arg335Trp	rs28371685

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines
Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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References

1. EXTENDED PHENYTOIN SODIUM- phenytoin sodium capsule [package insert]. Bridgewater, NJ: Amneal Pharmaceuticals of New York, L.; 2015. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7e467c02-49a0-4b62-b537-430fdfa4f10e
2. Caudle K.E., Rettie A.E., Whirl-Carrillo M., Smith L.H., et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharmacol Ther. 2014;96(5):542–8. PubMed PMID: 25099164.
3. Caudle K.E., Dunnenberger H.M., Freimuth R.R., Peterson J.F., et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2016. PubMed PMID: 27441996.
4. Catterall W.A. Molecular properties of brain sodium channels: an important target for anticonvulsant drugs. Adv Neurol. 1999;79:441–56. PubMed PMID: 10514834.
5. Lipkind G.M., Fozzard H.A. Molecular model of anticonvulsant drug binding to the voltage-gated sodium channel inner pore. Mol Pharmacol. 2010;78(4):631–8. PubMed PMID: 20643904.
6. Segal M.M., Douglas A.F. Late sodium channel openings underlying epileptiform activity are preferentially diminished by the anticonvulsant phenytoin. J Neurophysiol. 1997;77(6):3021–34. PubMed PMID: 9212254.
7. *Birth Defects: Data & Statistics*. Centers for Disease Control and Prevention (CDC); Available from: http://www.cdc.gov/ncbddd/birthdefects/data.html.

8. Hill D.S., Wlodarczyk B.J., Palacios A.M., Finnell R.H. Teratogenic effects of antiepileptic drugs. Expert Rev Neurother. 2010;10(6):943–59. PubMed PMID: 20518610.
9. Svensson C.K., Cowen E.W., Gaspari A.A. Cutaneous drug reactions. Pharmacological reviews. 2001;53(3):357–79. PubMed PMID: 11546834.
10. Nomenclature for Factors of the HLA System: HLA Alleles 2016 [Cited 23 June 2016]. Available from: http://hla.alleles.org/alleles/index.html
11. Choo S.Y. The HLA system: genetics, immunology, clinical testing, and clinical implications. Yonsei Med J. 2007;48(1):11–23. PubMed PMID: 17326240.
12. Chung W.H., Hung S.I., Hong H.S., Hsih M.S., et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004;428(6982):486. PubMed PMID: 15057820.
13. Amstutz U., Shear N.H., Rieder M.J., Hwang S., et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia. 2014;55(4):496–506. PubMed PMID: 24597466.
14. Locharernkul C., Loplumlert J., Limotai C., Korkij W., et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. Epilepsia. 2008;49(12):2087–91. PubMed PMID: 18637831.
15. Hung S.I., Chung W.H., Liu Z.S., Chen C.H., et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics. 2010;11(3):349–56. PubMed PMID: 20235791.
16. TEGRETOL (carbamazepine) tablet [package insert]. East Hanover, New Jersey 07936: Corporation, N.P.; 2011. Available from: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=8d409411-aa9f-4f3a-a52c-fbcb0c3ec053
17. Leckband S.G., Kelsoe J.R., Dunnenberger H.M., George A.L. Jr, et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clinical pharmacology and therapeutics. 2013;94(3):324–8. PubMed PMID: 23695185.
18. Chung W.H., Hung S.I., Chen Y.T. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. Expert Opin Drug Saf. 2010;9(1):15–21. PubMed PMID: 20001755.
19. Puangpetch A., Koomdee N., Chamnanphol M., Jantararoungtong T., et al. HLA-B allele and haplotype diversity among Thai patients identified by PCR-SSOP: evidence for high risk of drug-induced hypersensitivity. Front Genet. 2014;5:478. PubMed PMID: 25657656.
20. Nguyen D.V., Chu H.C., Nguyen D.V., Phan M.H., et al. HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. Asia Pac Allergy. 2015;5(2):68–77. PubMed PMID: 25938071.
21. Chong K.W., Chan D.W., Cheung Y.B., Ching L.K., et al. Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B*1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore. Arch Dis Child. 2014;99(6):581–4. PubMed PMID: 24225276.
22. Hung S.I., Chung W.H., Jee S.H., Chen W.C., et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006;16(4):297–306. PubMed PMID: 16538176.
23. Lonjou C., Thomas L., Borot N., Ledger N., et al. A marker for Stevens-Johnson syndrome ...: ethnicity matters. Pharmacogenomics J. 2006;6(4):265–8. PubMed PMID: 16415921.
24. Alfirevic A., Jorgensen A.L., Williamson P.R., Chadwick D.W., et al. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. Pharmacogenomics. 2006;7(6):813–8. PubMed PMID: 16981842.
25. Kaniwa N., Saito Y., Aihara M., Matsunaga K., et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. Pharmacogenomics. 2008;9(11):1617–22. PubMed PMID: 19018717.
26. Mehta T.Y., Prajapati L.M., Mittal B., Joshi C.G., et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. Indian J Dermatol Venereol Leprol. 2009;75(6):579–82. PubMed PMID: 19915237.

27. Wu X.T., Hu F.Y., An D.M., Yan B., et al. Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. Epilepsy Behav. 2010;19(3):405–8. PubMed PMID: 20833111.
28. Sistonen J., Fuselli S., Palo J.U., Chauhan N., et al. Pharmacogenetic variation at CYP2C9, CYP2C19, and CYP2D6 at global and microgeographic scales. Pharmacogenetics and genomics. 2009;19(2):170–9. PubMed PMID: 19151603.
29. Solus J.F., Arietta B.J., Harris J.R., Sexton D.P., et al. Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics. 2004;5(7):895–931. PubMed PMID: 15469410.
30. Lee C.R., Goldstein J.A., Pieper J.A. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. Pharmacogenetics. 2002;12(3):251–63. PubMed PMID: 11927841.
31. Allabi A.C., Gala J.L., Horsmans Y. CYP2C9, CYP2C19, ABCB1 (MDR1) genetic polymorphisms and phenytoin metabolism in a Black Beninese population. Pharmacogenet Genomics. 2005;15(11):779–86. PubMed PMID: 16220110.
32. de Bakker P.I., McVean G., Sabeti P.C., Miretti M.M., et al. A high-resolution HLA and SNP haplotype map for disease association studies in the extended human MHC. Nat Genet. 2006;38(10):1166–72. PubMed PMID: 16998491.

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