Carbamazepine Therapy and *HLA* Genotypes

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Introduction

Carbamazepine is an antiseizure drug used in the treatment of epilepsy. It is also used to relieve pain in trigeminal neuralgia and is used to treat bipolar disorder (1, 2).

The human leukocyte antigens A and B (HLA-A and HLA-B) play an important role in how the immune system recognizes and responds to pathogens. HLA-A and -B belong to a class of molecules that are found on the surface of most cells. These molecules are responsible for presenting peptides to immune cells. Peptides derived from normal human proteins are recognized as such, whereas foreign peptides derived from pathogens trigger an immune response whose goal is to dispose of the pathogen or foreign body.

The genes encoding HLA-A and -B are among the most polymorphic genes in the human genome, and certain variant alleles can influence an individual's response to medication. *HLA-B*15:02* is a variant allele that occurs most commonly in individuals of Southeast Asian descent. Carriers of *HLA-B*15:02* are at a high risk of developing Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), a severe, and sometimes fatal, cutaneous hypersensitivity reaction, while taking carbamazepine (Table 1).

Individuals most likely to carry *HLA-B*15:02* are those of Han Chinese descent, followed by those in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong (3). Another HLA variant, *HLA-A*31:01*, which is present more globally, may also be a risk factor for other carbamazepine-induced hypersensitivity reactions, such as drug-induced hypersensitivity syndrome (HSS) or maculopapular exanthema (MPE) (2).

The FDA recommends that patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B*15:02* prior to initiating treatment with

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carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk (1). The Clinical Pharmacogenetics Implementation Consortium (CPIC) cautions that many people may be unaware of, or fail to disclose, more distant Asian ancestry in their families, a fact that the healthcare professional needs to be aware of. CPIC also points out that both children and adults are at risk (3).

Table 1. *HLA-B* genotype and the therapeutic recommendations for carbamazepine therapy

Genotype	Phenotypic implications	Therapeutic recommendations	Classification of recommendations
Noncarrier of *HLA-B*15:02*	Normal or reduced risk of carbamazepine-induced SJS/TEN	Use carbamazepine per standard dosing guidelines	Strong
Carrier of *HLA-B*15:02*	Increased risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naive, do not use carbamazepine*	Strong
		If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine	Optional

Noncarrier of *HLA-B*15:02*: No **1502* alleles reported, often reported as "negative" on a genotyping test.
Carrier of *HLA-B*15:02*: One or two **1502* alleles, often reported as "positive" on a genotyping test.
SJS/TEN: Stevens–Johnson syndrome/toxic epidermal necrolysis.
* Alternative medications such as phenytoin, fosphenytoin, 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 carbamazepine.
Table is adapted from Leckband SG, Kelsoe JR, Dunnenberger HM, George AL Jr, Tran E, Berger R, Müller DJ, Whirl-Carrillo M, Caudle KE, Pirmohamed M. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and carbamazepine dosing. Clinical pharmacology and therapeutics. 2013:94(3):324-8 (3).

Drug: Carbamazepine

Carbamazepine is an antiseizure drug used in the treatment of epilepsy. Carbamazepine is also used as analgesic in trigeminal neuralgia, and may be used in the treatment of bipolar disorder (2, 4).

Epilepsy is characterized by spontaneous recurrent epileptic seizures, which may be classified as focal or generalized. The symptoms of focal seizures depend upon where the focus of the seizure originates in the brain e.g., jerking of a limb indicates a focus in the contralateral motor cortex. In contrast, generalized seizures appear to originate in all regions of the cortex simultaneously and include absence seizures (sudden impaired consciousness and staring) and general tonic-clonic seizures (loss of consciousness,

stiffening of limbs in the tonic phase, and twitching or jerking muscles in the clonic phase).

Recent guidelines for the treatment of epilepsy recommend carbamazepine as one of the first-line treatments for focal seizures in adults, adolescents, and children; and also as drug for consideration in the treatment of general tonic-clonic seizures (2, 5).

Carbamazepine is a tricyclic compound that belongs to the class of antiseizure drugs that act by blocking voltage-dependent sodium channels present on neuronal cell membranes. Carbamazepine stabilizes the sodium channel in the inactivated state, leaving fewer of the channels available to open. This prolonged inactivated phase of the channel inhibits the rapid and repetitive generation of action potentials in the epileptic focus (3, 6).

Carbamazepine is metabolized in the liver by the cytochrome P-450 (CYP) system. The major metabolite is carbamazepine-epoxide, which has an anticonvulsant activity of uncertain significance. CYP3A4 is the main enzyme involved in the metabolism of carbamazepine; a lesser role is played by CYP2C8 and possibly CYP3A5. Minor metabolic pathways include multiple CYP enzymes, such as CYP2B6.

Carbamazepine stimulates transcriptional upregulation of CYP3A4 and other genes involved in its own metabolism. In addition, there are many drug-drug interactions with carbamazepine, because numerous drugs have been shown to induce or inhibit CYP3A4, or are metabolized by CYP3A4. Therefore, when carbamazepine is given with drugs that can decrease or increase carbamazepine levels, close monitoring of carbamazepine levels is indicated and dosage adjustment may be required (7, 8).

Carbamazepine-induced Adverse Drug Reactions

In general, there are two categories of adverse drug reactions. Type A reactions account for up to 85-90% of all adverse drug reactions. They are predictable based on the known properties of the drug, and they can affect any individual, if their exposure to the drug is high enough. For carbamazepine, type A adverse effects include sedation, CNS depression, and vestibular symptoms such as nystagmus and ataxia.

Type B reactions account for the remaining 10-15% of adverse drug reactions. These include hypersensitivity reactions that occur in susceptible individuals. Such idiosyncratic hypersensitivity reactions can occur at any dose and develop through a mechanism that is unrelated to the mechanism of action of the drug. For this reason, it is difficult to predict in whom a drug-induced hypersensitivity reaction is likely to occur. For carbamazepine, however, carriers of specific HLA variants are known to be susceptible to carbamazepine-induced hypersensitivity reactions, and HLA testing of patients can identify those at-risk individuals so that an alternative drug can be used.

Carbamazepine-induced hypersensitivity reactions frequently involve the skin. Cutaneous adverse drug reactions (cADR) are experienced by approximately 5-10% of patients taking carbamazepine. Most of these carbamazepine-induced cutaneous reactions are considered to be mild, such as maculopapular exanthema (MPE) and erythema

multiforme. Nevertheless, these cutaneous reactions can cause considerable discomfort to the patient and often lead to the discontinuation of carbamazepine therapy (2, 9, 10). Due to their structural similarity, up to 80% of patients who have an unexpected adverse reaction to carbamazepine will also have an adverse reaction to other anticonvulsants, thereby restricting treatment options (11).

More rarely, the use of carbamazepine can trigger serious hypersensitivity reactions, such as Stevens-Johnson syndrome (SJS) and the more severe form, toxic epidermal necrolysis (TEN) (12). SJS /TEN are life-threatening conditions that are primarily characterized by lesions of the skin (detachment of the epidermis) and mucus membranes (severe erosions) (12). SJS/TEN occurs in approximately 1-10 per 10,000 patients taking carbamazepine. Onset is delayed and may occur several weeks after the initiation of carbamazepine therapy. The mortality rate is high—up to 10% for SJS, and 50% for TEN (12-14).

Other severe and potentially life-threatening carbamazepine-induced hypersensitivity reactions include drug-induced hypersensitivity syndrome (HSS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS); and acute generalized exanthematous pustulosis (AGEP).

The mechanisms underlying these hypersensitivity reactions are largely unknown, but they are thought to involve the drug, or a molecule derived from the drug, interacting with the major histocompatibility complex (MHC) expressed on the surface of cells, resulting in a stimulation of the immune system, particularly T cells and eosinophils (2, 14).

HLA gene family

The human leukocyte antigen *(*HLA*)* genes are members of the MHC gene family, which includes more than 200 genes. The MHC family has been subdivided in to 3 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 of 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 (15). Each HLA allele has a name that is prefixed by HLA, followed by the gene name, an asterisk and a two digit number that corresponds to antigen specificity, and the assigned allele number (16). For example, for the allele *HLA-DRB1*13:01* is composed of:

- HLA: the HLA prefix (the HLA region on chromosome 6)
- DRB1: the DRB1 gene (a particular HLA gene in this region)
- 13: the allele group (historically determined by serotyping, i.e., a group of alleles that share the same serotype)
- 01: 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 the 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 the susceptibility to Type B adverse drug reactions, including carbamazepine hypersensitivity reactions. Specifically, two HLA variants have been found to be associated with carbamazepine-induced hypersensitivity reactions: *HLA-B*15:02* and *HLA-A*31:01*.

*HLA-B*15:02*

The association between the *HLA-B*15:02* allele and carbamazepine-induced SJS/TEN was first reported in the Han Chinese. In the initial study, every patient who had carbamazepine-induced SJS/TEN was found to be a carrier of the *HLA-B*15:02* allele (44/44, 100%), whereas the allele was much less common in carbamazepine-tolerant patients (3/101, 3%)(17). In subsequent studies, this strong association was replicated, with a *HLA-B*15:02* carrier frequency of between 70100% among cases of carbamazepine-induced SJS/TEN (2).

The *HLA-B*15:02* allele frequency is highest in Southeast Asia, and the prevalence of carbamazepine-induced SJS/TEN is higher in populations where *HLA-B*15:02* is common. The *HLA*15:02* allele is strongly associated with carbamazepine-induced SJS/TEN in Taiwanese, Chinese, Indians, Malay, and Chinese-Americans, but not in Caucasians or Japanese individuals (17-24).

In Hong Kong, Thailand, Malaysia, Vietnam, and parts of the Philippines, the allele frequency is over 15%; it is slightly lower (around 10-13%) in Taiwan and Singapore, and around 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of *HLA-B*15:02*, averaging 2 to 4%, with higher frequencies in some subpopulations (1-3, 25-28).

The *HLA-B*15:02* allele is rare (carrier frequency of less than 1%) in East Asia (Japan and Korea) and in individuals who are not of Asian descent. For example, the variant is very rare in Europeans, Hispanics, Africans, African Americans, and Native Americans (2, 25). The absence of this variant in these population explains the lack of association of this variant with carbamazepine-induced SJS/TEN in Caucasians and Japanese individuals.

Current data suggest that *HLA-B*15:02* is a risk factor specific to SJS/TEN since it does not appear to increase the risk of other carbamazepine-induced cutaneous reactions, such as maculopapular exanthema or the carbamazepine-induced hypersensitivity syndrome (2).

*HLA-A*31:01*

The *HLA-A*31:01* allele has been consistently associated with carbamazepine-induced hypersensitivity syndrome and maculopapular exanthema (MPE) in Europeans, Han Chinese, Japanese, and North Americans of mixed ancestries (13, 18, 29-31). This variant may also be associated with SJS/TEN but so far the association has been inconsistent (2).

Whereas the *HLA-B*15:02* allele is mainly found in individuals of Asian descent, the *HLA-A*31:01* variant is common globally with carrier frequencies of at least 3% in many populations (2-5% in Northern Europeans, 2% in Han Chinese, 9% in Japanese populations) (2, 13, 30).

Genetic Testing

Genetic testing is available for *HLA-B*15:02* and *HLA-A*31:01*. The genotype results for an HLA allele such as *HLA-B*15:02* can either be "positive" (the HLA allele being present in one or both copies of the gene) or "negative" (no copies of HLA allele are present). There are no intermediate phenotypes because the HLA genes are expressed in a codominant manner (15).

Therapeutic Recommendations based on Genotype

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

Statement from the US Food and Drug Administration (FDA): Serious and sometimes fatal dermatologic reactions, including toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS), have been reported during treatment with carbamazepine. These reactions are estimated to occur in 1 to 6 per 10,000 new users in countries with mainly

[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 labelled all formulations containing the generic drug.

Caucasian populations, but the risk in some Asian countries is estimated to be about 10 times higher. 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. *HLA-B*1502* is found almost exclusively in patients with ancestry across broad areas of Asia. Patients with ancestry in genetically at-risk populations should be screened for the presence of *HLA-B *1502* prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk.

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

Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC): Currently, the Food and Drug Administration recommends that "patients with ancestry in at-risk populations should be screened for the presence of *HLA-B*1502* allele prior to starting carbamazepine". Individuals at highest risk are those of Han Chinese descent, followed by those in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong. The frequency of *HLA-B*15:02* is very low in other populations. However, it is important that the prescribing physician bear in mind that many people may be unaware of or fail to disclose more distant Asian ancestry in their families. In addition, much of the evidence linking *HLA-B*15:02* to SJS/TEN was generated in both children and adults. Therefore, regardless of ancestry or age of the individual, if the genetic testing results are "positive" for the presence of at least one copy of the *HLA-B*15:02* allele, it is recommended that a different agent be used depending on the underlying disease, unless the benefits clearly outweigh the risk (Table 1).

Carbamazepine-induced SJS/TEN usually develops within the first 3 months of therapy; therefore, patients who have been taking carbamazepine for longer than 3 months without developing cutaneous reactions are at low risk (but not zero) of carbamazepine-induced adverse events in the future, regardless of *HLA-B*15:02* status.

Please review the complete therapeutic recommendations that are located here: (3).

Recommendations from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS):

Recommendation 1.1: Genetic testing for *HLA- B*15:02* is recommended for all CBZ-naive patients before initiation of CBZ therapy (Level A – strong in patients originating from populations where *HLA- B*15:02* is common, its frequency unknown or whose origin is unknown; Level C – optional in patients originating from populations where *HLA-B*15:02* is rare). Genetic testing for *HLA-A*31:01* is recommended for all CBZ-naive patients before initiation of CBZ therapy (Level B – moderate in all patients; Table 2).

Recommendation 1.2: In patients who have previously taken CBZ for > 3 months without any adverse effects, and in whom reinitiation of CBZ is considered, genetic testing is NOT recommended (B). In patients who have previously taken CBZ for a shorter period, genetic testing should be considered (B).

Recommendation 1.3: In patients who have previously experienced a HSR potentially related to CBZ, genetic testing is recommended as part of the differential diagnosis and for the direction of future therapy (B).

Recommendation 1.4: In patients for whom no alternative treatment options are available, genetic testing is recommended to ensure increased alertness to hypersensitivity symptoms in positive patients (B).

Recommendation 2.1: Genetic testing for *HLA- B*15:02* is most beneficial in patients originating from a population where *HLA-B*15:02* is common (e.g., Chinese, Thai, Indian, Malay, Filipino, Indonesian; A). Nevertheless, genotyping for *HLA-B*15:02* should be considered in ALL patients, irrespective of their ancestry, as the safest option (C).

Recommendation 2.2: *HLA-A*31:01* is common in most populations studied so far. Therefore, genetic testing for this variant is recommended in patients of all ancestries (B).

Recommendation 3.1: In patients who are positive for *HLA-B*15:02* or *HLA-A*31:01*, alternative medications should be used as first-line therapy (A). Consideration in the choice of alternative medications should be given to the possibility of cross-reactivity with structurally similar AEDs (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, primidone).

Recommendation 3.2: In patients who are negative for *HLA-B*15:02* and *HLA-A*31:01*, CBZ can be used as first-line therapy (A). However, the occurrence of a HSR cannot be excluded based on a negative genetic test result.

Table 2. Grading scheme used for clinical practice recommendations

Level	Strength	Evidence basis
A	Strong	Based on strong scientific evidence; benefits clearly outweigh risks
B	Moderate	Based on reduced confidence scientific evidence and expert opinion; benefits likely to outweigh risks
C	Optional	Based mainly on expert opinion, for use with evidence development in a research context

Table adapted from: Amstutz, U., N.H. Shear, M.J. Rieder, S. Hwang, 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): p. 496-506 (2).

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

Nomenclature

Allele name	dbSNP reference identifier for allele location
*HLA-B*15:02*	rs2844682 and rs3909184**
*HLA-A*31:01*	rs1061235 and rs16333021**

* 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 (32).
** Because of the extreme diversity at the HLA locus, different tag SNPs may be associated with different HLA variants in different populations. For *HLA-B*15:02*, rs2844682 and rs3909184 are the tag SNPs (33). For *HLA-A*31:01*, rs1061235 is a tag SNP in Europeans (13) and rs16333021 is a tag SNP in Japanese (29). A study involving North American children of various ancestries showed that rs1061235 is not a suitable tag SNP in non-Caucasian individuals (30).

Guidelines on nomenclature of the HLA system are available from HLA Nomenclature: http://hla.alleles.org/

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References

1. 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
2. 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.
3. 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.
4. DrugBank [Internet]. Edmonton, AB, Canada: University of Alberta. Carbamazepine. [Cited 2012 August 28]. Available from: http://www.drugbank.ca/drugs/DB00564
5. National Clinical Guideline Centre (UK). The Epilepsies: The Diagnosis and Management of the Epilepsies in Adults and Children in Primary and Secondary Care: Pharmacological Update of Clinical Guideline 20. (NICE Clinical Guidelines, No. 137). [Cited July 2015]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK247130/

6. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Drug/Small Molecule: Carbamazepine. [Cited 2012 August 28]. Available from: http://www.pharmgkb.org/drug/PA448785
7. Pearce R.E., Lu W., Wang Y., Uetrecht J.P., et al. Pathways of carbamazepine bioactivation in vitro. III. The role of human cytochrome P450 enzymes in the formation of 2,3-dihydroxycarbamazepine. Drug metabolism and disposition: the biological fate of chemicals. 2008;36(8):1637–49. PubMed PMID: 18463198.
8. PharmGKB [Internet]. Palo Alto (CA): Stanford University. Pathway: Carbamazepine Pathway, Pharmacokinetics [Cited 2012 August 27]. Available from: http://www.pharmgkb.org/pathway/PA165817070
9. Hirsch L.J., Arif H., Nahm E.A., Buchsbaum R., et al. Cross-sensitivity of skin rashes with antiepileptic drug use. Neurology. 2008;71(19):1527–34. PubMed PMID: 18981374.
10. Yang F., Yang Y., Zhu Q., Chen S.A., et al. Research on Susceptible Genes and Immunological Pathogenesis of Cutaneous Adverse Drug Reactions in Chinese Hans. J Investig Dermatol Symp Proc. 2015;17(1):29–31. PubMed PMID: 26067314.
11. Shear N.H., Spielberg S.P. Anticonvulsant hypersensitivity syndrome. In vitro assessment of risk. J Clin Invest. 1988;82(6):1826–32. PubMed PMID: 3198757.
12. Pirmohamed M., Friedmann P.S., Molokhia M., Loke Y.K., et al. Phenotype standardization for immune-mediated drug-induced skin injury. Clin Pharmacol Ther. 2011;89(6):896–901. PubMed PMID: 21562486.
13. McCormack M., Alfirevic A., Bourgeois S., Farrell J.J., et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011;364(12):1134–43. PubMed PMID: 21428769.
14. Pavlos R., Mallal S., Ostrov D., Buus S., et al. T cell-mediated hypersensitivity reactions to drugs. Annu Rev Med. 2015;66:439–54. PubMed PMID: 25386935.
15. Martin M.A., Klein T.E., Dong B.J., Pirmohamed M., et al. Clinical pharmacogenetics implementation consortium guidelines for HLA-B genotype and abacavir dosing. Clinical pharmacology and therapeutics. 2012;91(4):734–8. PubMed PMID: 22378157.
16. Choo S.Y. The HLA system: genetics, immunology, clinical testing, and clinical implications. Yonsei Med J. 2007;48(1):11–23. PubMed PMID: 17326240.
17. 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.
18. 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.
19. 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.
20. 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.

21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. Ozeki T., Mushiroda T., Yowang A., Takahashi A., et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. Hum Mol Genet. 2011;20(5):1034–41. PubMed PMID: 21149285.
30. Amstutz U., Ross C.J., Castro-Pastrana L.I., Rieder M.J., et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. Clin Pharmacol Ther. 2013;94(1):142–9. PubMed PMID: 23588310.
31. Genin E., Chen D.P., Hung S.I., Sekula P., et al. HLA-A*31:01 and different types of carbamazepine-induced severe cutaneous adverse reactions: an international study and meta-analysis. Pharmacogenomics J. 2014;14(3):281–8. PubMed PMID: 24322785.
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. Nature genetics. 2006;38(10):1166–72. PubMed PMID: 16998491.
33. 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.

Related Summaries by Gene

Abacavir Therapy and *HLA-B*57:01* Genotype

Allopurinol Therapy and *HLA-B*58:01* Genotype

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

Related Summaries by Drug Class

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

Tests in GTR by Condition

Carbamazepine response

Carbamazepine hypersensitivity

Tests in GTR by Gene

HLA-B gene

HLA-A gene