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Carbamazepine Therapy and *HLA* Genotype

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Introduction

Carbamazepine (brand names include Carbatrol, Epitol, Equetro, and Tegretol) is an effective antiseizure drug that is often used as a first-line agent in the treatment of epilepsy. Carbamazepine is also used to treat bipolar disorder and to relieve pain in trigeminal neuralgia.

Hypersensitivity reactions associated with carbamazepine can occur in up to 10% of patients, and typically affect the skin. Some of these reactions are mild, as in the case of maculopapular exanthema (MPE); however, conditions such as Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life-threatening.

The risk of hypersensitivity is increased by the presence of specific human leukocyte antigen (*HLA)* alleles. The *HLA-B*15:02* allele is strongly associated with carbamazepine-induced SJS/TEN in populations where this allele is most common, such as in Southeast Asia.

According to the FDA-approved drug label for carbamazepine, testing for *HLA-B*15:02* should be done for all patients with ancestry in populations with increased frequency of *HLA-B*15:02*, prior to initiating carbamazepine therapy (Table 1). The label states that greater than 15% of the population is reported *HLA-B*15:02* positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. The label states that South Asians, including Indians, appear to have intermediate prevalence of *HLA-B*15:02*, averaging 2 to 4%, but higher in some groups. In Japan and Korea, the *HLA- B*15:02* is present in less than 1% of the population. In individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans), the *HLA-B*15:02* allele is largely absent. These prevalence rates of *HLA-B*15:02* may be used to guide which patients should be screened. However, the FDA cautions to keep in mind the limitations of prevalence rate data when deciding which patients to screen. This is because of the wide variability in *HLA-B*15:02* rates (even within ethnic groups), the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry (1).

The FDA label also states that carbamazepine should not be used in patients who are positive for *HLA-B*15:02* unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN.

The *HLA-A*31:01* allele may also be a risk factor for SJS/TEN but is more strongly associated with other carbamazepine-induced reactions, such as DRESS and MPE. *HLA-A*31:01* is found in most populations, worldwide. *HLA-B*15:11* is another allele that has been linked with SJS/TEN. The FDA states that the risks and

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benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for *HLA-A*31:01*, but does not discuss *HLA-B*15:11* (1).

Carbamazepine dosing guidelines based on *HLA* genotype have been published by the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), the Clinical Pharmacogenetics Implementation Consortium (CPIC), and the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) (2-5).

DPWG recommendations include avoiding the use of carbamazepine and selecting an alternative, if possible, for individuals positive for *HLA-B*15:02*, *HLA-A*31:01* and *HLA-B*15:11* (Table 2). CPIC recommendations include not using carbamazepine in carbamazepine-naïve patients who are positive for *HLA-B*15:02* and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown) (Table 3). CPNDS recommends genetic testing for all carbamazepine-naïve patients before they start treatment, with a moderate level of evidence for *HLA-A*31:01* testing, and strong to optional evidence for *HLA-B*15:02* testing (based on the frequency of *HLA-B*15:02* in the population the patient originates from, and if this is known or not) (Table 4).

Table 1. FDA (2018) Drug Label for Carbamazepine. Recommendations for *HLA-B*15:02* and *HLA-A*31:01* Genotype: Warnings.

Genotype	Recommendations
SJS/TEN and *HLA-B*15:02* Allele	Prior to initiating carbamazepine therapy, testing for *HLA-B*15:02* should be performed in patients with ancestry in populations in which *HLA-B*15:02* may be present. Carbamazepine should not be used in patients positive for *HLA-B*15:02* unless the benefits clearly outweigh the risks.
Hypersensitivity Reactions and *HLA-A*31:01* Allele	The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for *HLA-A*31:01*.

Please see Therapeutic Recommendations based on Genotype for more information from the FDA. This table is adapted from (1).

Table 2. DPWG (2017) Recommendations for Carbamazepine and *HLA* Genotype.

Genotype	Recommendations
*HLA-B*15:02* positive	Choose an alternative if possible
*HLA-A*31:01* positive	1. carefully weigh the risk of DRESS and SJS/TEN against the benefits 2. if an alternative is an option, choose an alternative
*HLA-B*15:11* positive	1. carefully weigh the risk of SJS/TEN against the benefits 2. if an alternative is an option, choose an alternative

Please see Therapeutic Recommendations based on Genotype for more information from DPWG. This table is adapted from (2).

Table 3. CPIC (2016) Recommendations for Carbamazepine Therapy based on *HLA-B* and *HLA-A* Genotype.

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendations	Considerations for other aromatic anticonvulsants
*HLA-B*15:02* negative and *HLA-A*31:01* negative	Normal risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	Use carbamazepine per standard dosing guidelines.[b]	Strong	N/A
*HLA-B*15:02* negative and *HLA-A*31:01* positive	Greater risk of carbamazepine-induced SJS/TEN, DRESS, and MPE	If patient is carbamazepine-naïve and alternative agents are available, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have very limited evidence, if any, linking SJS/ TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic

Table 3. continued from previous page.

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendations	Considerations for other aromatic anticonvulsants
				anticonvulsant as an alternative agent.
		If patient is carbamazepine-naïve and alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at first evidence of a cutaneous adverse reaction.	Optional	N/A
		The latency period for cutaneous adverse drug reactions is variable depending on phenotype; however, all usually occur within three months of regular dosing. Therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]
*HLA-B*15:02* positive[c] and any *HLA-A*31:01* genotype (or *HLA-A*31:01* genotype unknown)	Greater risk of carbamazepine-induced SJS/TEN	If patient is carbamazepine-naïve, do not use carbamazepine.	Strong	Other aromatic anticonvulsants[d] have weaker evidence linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used in choosing an alternative agent.

Table 3. continued from previous page.

Genotype[a]	Implication	Therapeutic recommendation	Classification of recommendations	Considerations for other aromatic anticonvulsants
		The latency period for drug-induced SJS/TEN is short with continuous dosing and adherence to therapy (4-28 days), and cases usually occur within three months of dosing; therefore, if the patient has previously used carbamazepine consistently for longer than three months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine in the future.	Optional	Previous tolerance of carbamazepine is not indicative of tolerance to other aromatic anticonvulsants.[d]

DRESS, drug reaction with eosinophilia and systemic symptoms; MPE, maculopapular exanthema; N/A, not applicable; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[a]If only *HLA-B*15:02* was tested, assume *HLA-A**31:01 is negative and vice versa.
[b]*HLA-B*15:02* has a 100% negative predictive value for carbamazepine-induced SJS/ TEN, and its use is currently recommended to guide the use of carbamazepine and oxcarbazepine only. Because there is a much weaker association and less than 100% negative predictive value of *HLA-B*15:02* for SJS/TEN associated with other aromatic anticonvulsants, using these drugs instead of carbamazepine or oxcarbazepine in the setting of a negative *HLA-B*15:02* test in Southeast Asians will not result in prevention of anticonvulsant-associated SJS/TEN.
[c]In addition to *HLA-B*15:02*, the risk for carbamazepine-induced SJS/TEN has been reported in association with the most common B75 serotype alleles in Southeast Asia, *HLA-B**15:08, *HLA-B*15:11*, and *HLA- B*15:21*. Although not described, the possibility of carbamazepine-induced SJS/TEN in association with less frequently carried B75 serotype alleles, such as *HLA- B**15*:30* and *HLA-B*15:31*, should also be considered.
[d]Aromatic anticonvulsants include carbamazepine, oxcarbazepine, eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital.
This table is adapted from Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, Goldspiel B, Chen YT, Carleton BC, George ALJ, Mushiroda T, Klein T, Gammal RS, and Pirmohamed M. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clinical pharmacology and therapeutics (4).

Table 4. CPNDS (2014) Recommendations for Carbamazepine and *HLA* Genotype.

Genotype	Recommendation 1.1
*HLA-B*15:02*	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).
*HLA-A*31:01*	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 7).

CBZ: Carbamazepine.
Please see Therapeutic Recommendations based on Genotype for the all the recommendations from CPNDS, and the grading scheme used for the level of evidence. Table is adapted from (5).

Drug: Carbamazepine

Carbamazepine is an antiseizure drug used in the treatment of epilepsy. Carbamazepine is also used as an analgesic in trigeminal neuralgia and may be used in the treatment of bipolar disorder (5, 7, 8).

Epilepsy is characterized by spontaneous recurrent epileptic seizures, which may be classified as focal or generalized. Carbamazepine is one of the first-line treatments for focal seizures in adults, adolescents, and children, and it may also be considered for general tonic-clonic seizures.

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).

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, 9).

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 (10, 11).

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 reactions are difficult to predict (idiosyncratic) because they can occur at any dose, and they develop through a mechanism that is unrelated to the mechanism of action of the drug. For carbamazepine, type B adverse reactions include carbamazepine-induced hypersensitivity reactions that typically involve the skin.

Approximately 5–10% of patients taking carbamazepine will experience carbamazepine-induced cutaneous reactions. Most of these are considered to be mild, such as maculopapular exanthema (MPE) and erythema multiforme. However, these cutaneous reactions can cause considerable discomfort to the patient and often lead to the discontinuation of carbamazepine therapy (5, 12, 13). In addition, treatment may be stopped because of the risk of a more severe, cutaneous drug reaction developing.

Stevens-Johnson syndrome (SJS) and the more severe form, toxic epidermal necrolysis (TEN), can be induced by carbamazepine therapy. These are life-threatening conditions that are primarily characterized by lesions of the skin (detachment of the epidermis) and mucous membranes (severe erosions) (11). 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 (11, 14, 15). Pediatric patients who survive SJS/TEN usually have long-term complications, such as scarring, visual loss and chronic kidney disease (16).

Another severe and potentially life-threatening carbamazepine-induced hypersensitivity reaction is known as drug reaction with eosinophilia and systemic symptoms (DRESS, also known as drug-induced hypersensitivity syndrome, HSS).

The mechanisms underlying this hypersensitivity reaction is poorly understood, but is 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 (5, 15).

Individuals who have specific *HLA* variants are known to be susceptible to carbamazepine-induced hypersensitivity reactions. In 2007, the FDA added a warning to the drug label concerning carbamazepine-induced SJS/TEN, with a recommendation for *HLA-B*15:02* screening in South-East Asian populations (17). Carbamazepine should not be used in patients who have the *HLA-B*15:02* variant (Table 1).

Screening of patients prior to carbamazepine therapy can identify those at higher risk of hypersensitivity reactions, allowing for an alternative drug to be used. Clinical practice guidelines for the treatment of epilepsy, bipolar disorder, and trigeminal neuralgia should be consulted for recommended alternative therapies to carbamazepine. However, caution should be used because of the risk of cross-reactivity between structurally similar antiseizure drugs (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, primidone) (5, 18).

Up to 80% of patients who have an unexpected adverse reaction to carbamazepine will also have an adverse reaction to other antiseizure drugs, thereby restricting treatment options (19). Phenytoin and lamotrigine have both been associated with carbamazepine-induced SJS/TEN, and some evidence also links fosphenytoin, oxcarbazepine, eslicarbazepine acetate with SJS/TEN (20).

HLA gene family

The human leukocyte antigen (*HLA*) genes code for more than 200 different major histocompatibility complex (MHC*)* proteins. 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 proteins encoded by the HLA genes *HLA-A, HLA-B, and HLA-C*. These MHC molecules are expressed on the surfaces of almost all cells and play an important role in processing and presenting antigens. The MHC 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 MHC 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 MHC 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 (7). 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 (21). 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., because of synonymous and noncoding genetic variants).

Variation in *HLA* genes plays an important role in the susceptibility to autoimmune disease and infections. 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 an increasing number of drug hypersensitivity responses (Type B adverse drug reactions). The strongest HLA-associated drug responses are *HLA-B*15:02* and carbamazepine-induced SJS/TEN in Asian populations, *HLA-B*57:01* and abacavir hypersensitivity syndrome in the Caucasian population, and *HLA-B*58:01* in allopurinol hypersensitivity syndrome and SJS/TEN (22).

Gene: HLA-B, Allele HLA-B*15:02

*HLA-B*15:02* is strongly associated with carbamazepine-induced SJS/TEN in populations where the *HLA-B*15:02* is common (China, Thailand, India, Malaysia, Taiwan). In patients of Asian origin, pharmacogenetic testing for *HLA-B*15:02* is recommended before initiation of carbamazepine therapy (23). The clinical benefits of screening for *HLA-B*15:02* have been confirmed in a Taiwanese study, where genetic testing reduced the incidence of carbamazepine-induced SJS/TEN from ten expected cases to zero (24).

The association between *HLA-B*15:02* and SJS/TEN was first reported in the Han Chinese. In the initial study, every patient who had carbamazepine-induced SJS/TEN was found to have the *HLA-B*15:02* allele (44/44, 100%), whereas the allele was much less common in carbamazepine-tolerant patients (3/101, 3%) (25). The *HLA*15:02* allele has since been associated with carbamazepine-induced SJS/TEN in Taiwanese, Chinese, Indians, Malay, and Chinese-Americans, but not in Caucasians or Japanese individuals (25-32).

The prevalence of carbamazepine-induced SJS/TEN is higher in populations where the *HLA-B*15:02* allele is most common. *HLA-B*15:02* is highly prevalent in Southeast Asia, with an allele frequency of over 15% in Hong Kong, Thailand, Malaysia, Vietnam, and parts of the Philippines. It is slightly less prevalent (10–13%) in Taiwan and Singapore, and in North China (4%). South Asians, including Indians, have intermediate prevalence of *HLA-B*15:02* (2–4%), with higher frequencies in some sub-populations (3, 5, 33-37).

The *HLA-B*15:02* allele is rare (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 rare in Europeans, Hispanics, Africans, African Americans, and Native Americans (5, 34). The absence of this variant in these population explains the lack of association of *HLA-B*15:02* with carbamazepine-induced SJS/TEN in Caucasians and Japanese individuals.

Current data suggest that *HLA-B*15:02* is a risk factor only for SJS/TEN because it does not appear to increase the risk of other carbamazepine-induced cutaneous reactions such as MPE and DRESS (5).

Gene: *HLA-A*, Allele *HLA-A*31:01*

The *HLA-A*31:01* allele is important for all types of carbamazepine hypersensitivity reactions. Also, in contrast to *HLA-B*15:02* which is predominantly found in Southeast Asia, the *HLA-A*31:01* is found in many populations worldwide (Table 5) (38-40).

Table 5. Comparison of *HLA-B*15:02* and *HLA-A*31:01* and Carbamazepine Therapy

	*HLA-B*15:02*	*HLA-A*31:01*
Associated phenotype	*HLA-B*15:02* is strongly associated with SJS/TEN	*HLA-A*31:01* is associated with all carbamazepine hypersensitivity phenotypes, including MPE, HSS, and (less strongly) SJS/TEN

Table 5. continued from previous page.

	*HLA-B*15:02*	*HLA-A*31:01*
Allele distribution	Predominantly concentrated in Southeast Asia, e.g., Hong Kong, Thailand, Malaysia, Vietnam, Philippines, Taiwan, Singapore.	Widely distributed across a range of populations including Europeans, Japanese, South Koreans and Han Chinese
Phenotype distribution	The strong association of *HLA-B*15:02* with carbamazepine-induced SJS/TEN is largely confined to individuals from Southeast Asian countries	*HLA-A*31:01* has been associated with carbamazepine-induced hypersensitivity reactions, particularly HSS, across different populations including European and Japanese individuals.
Pharmacogenetic screening recommendations	Screening for *HLA-B*15:02* is mandated in patients from Southeast Asia, prior to initiation of carbamazepine therapy. The FDA states 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 carbamazepine".	Screening is not currently mandated prior to initiation of carbamazepine therapy. The FDA states that the "risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for *HLA-A*31:01*".
Allele frequencies (reported by the FDA (1))	Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of *HLA-B*15:02*, averaging 2% to 4%, but higher in some groups. *HLA-B*15:02* is present in less than 1% of the population in Japan and Korea. *HLA-B*1502* is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).	*HLA-A*31:01* is expected to be positive by more than 15% of patients of Japanese, Native American, South Indian (for example, Tamil Nadu) and some Arabic ancestry; up to about 10% in patients of Han Chinese, Korean, European, Latin American, and other Indian ancestry; and up to about 5% in African- Americans and patients of Thai, Taiwanese, and Chinese (Hong Kong) ancestry.

SJS/TEN: Stevens–Johnson syndrome/ toxic epidermal necrolysis
MPE: maculopapular exanthema
HSS: drug-induced hypersensitivity syndrome

The association between *HLA-A*31:01* and DRESS and MPE has been found in Europeans, Han Chinese, Japanese, and North Americans of mixed ancestries (14, 26, 41-43). *HLA-A*31:01* is also associated with SJS/TEN, but not in Southeast Asians, where the more common HLA-B*15*:02* allele has an extremely strong association with SJS/TEN (5, 38).

The *HLA-A*31:01* variant is common globally with frequencies of at least 3% in many populations (2–5% in Northern Europeans, 2% in Han Chinese, 7–12% in Japanese populations) (5, 14, 38, 42). The highest frequencies have been reported in South American countries, such as Argentina (25%–38.6%) (38).

Gene: *HLA-B, HLA-B*15:11* and other alleles

The *HLA-B*15:11* variant has been found to be a risk factor for SJS/TEN in Japan (44, 45) and Korea (46). In Central China, *HLA-B*15:11* may be a risk factor for some patients with CBZ-induced SJS negative for *HLA-B*15:02* (47), and one study found that *HLA-A*11:01* for CBZ-induced SJS/TEN was a risk factor in the Spanish Caucasian population (39).

The *HLA-B*15:11* variant is found in frequencies above 1% in specific Asian populations only:Han Chinese, Koreans, Thai (34, 48).

Other alleles considered to be high risk, particularly in high-frequency areas such as Indonesia, Malaysia, and Thailand, include *HLA-B*15:08* and *HLA-B*15:21* (49, 50).

Genetic Testing

The NIH Genetic Testing Registry provides examples of the genetic tests that are currently available for the carbamazepine response, and the *HLA-B* and *HLA-A* genes.

The FDA recommends testing for *HLA-B*15:02* prior to initiating carbamazepine therapy in patients with ancestry in populations with increased frequency of *HLA-B*15:02*. In deciding which patients to screen, the FDA states that the prevalence rates of *HLA-B*15:02* (Table 1) may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry (1).

The genotype results for an *HLA* allele such as *HLA-B*15:02* can either be "positive" or "negative" (Table 6). There are no intermediate phenotypes because the HLA genes are expressed in a codominant manner. A positive result is either "heterozygous" or "homozygous", depending upon whether the patient has one or two copies of the **15:02* allele, respectively.

For patients who are positive for *HLA-B*15:02*, the FDA states that carbamazepine should not be used unless the benefits clearly outweigh the risks. For patients who are known to be positive for *HLA-A*31:01*, the FDA states that the risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine.

A negative result indicates that the patient does not have the *HLA-B*15:02* allele. However, a negative result does not rule out the possibility of a patient developing carbamazepine hypersensitivity. Therefore, clinicians should carefully monitor all patients according to standard practices.

Table 6. CPIC (2017). Assignment of likely *HLA-B and HLA-A* genotype

Genotype	Definition	Examples of diplotypes
*HLA-B*15:02* negative	Homozygous for an allele other than *HLA-A*15:02*	$*X/*X^a$
*HLA-B*15:02* positive	Heterozygous or homozygous variant	$*15:02/*X^a$, **15:02/*15:02*
*HLA-A*31:01* negative	Homozygous for an allele other than *HLA-A*31:01*	$*Y^b/*Y^b$
*HLA-A*31:01* positive	Heterozygous or homozygous variant	$31:01/*Y^b$, **31:01/*31:01*

[a] Where *X 5 any *HLA-B* allele other than *HLA-B*15:02*.
[b] Where *Y 5 any *HLA-A* allele other than *HLA-A*31:01*.
Table is adapted from Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, Goldspiel B, Chen YT, Carleton BC, George ALJ, Mushiroda T, Klein T, Gammal RS, and Pirmohamed M. Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clinical pharmacology and therapeutics (4).

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.

[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. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations where necessary, other author insertions are shown in square brackets.*

2018 Statement from the US Food and Drug Administration (FDA)

SJS/TEN and HLA-B*1502 Allele

Retrospective case-control studies have found that in patients of Chinese ancestry there is a strong association between the risk of developing SJS/TEN with carbamazepine treatment and the presence of an inherited variant of the *HLA*-B gene, *HLA-B*15:02*. The occurrence of higher rates of these reactions in countries with higher frequencies of this allele suggests that the risk may be increased in allele-positive individuals of any ethnicity.

Across Asian populations, notable variation exists in the prevalence of *HLA-B*15:02*. Greater than 15% of the population is reported positive in Hong Kong, Thailand, Malaysia, and parts of the Philippines, compared to about 10% in Taiwan and 4% in North China. South Asians, including Indians, appear to have intermediate prevalence of *HLA-B*1502*, averaging 2 to 4%, but higher in some groups. *HLA- B*15:02* is present in <1% of the population in Japan and Korea.

*HLA- B*15:02* is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans).

Prior to initiating carbamazepine therapy, testing for *HLA-B*15:02* should be performed in patients with ancestry in populations in which *HLA-B*15:02* may be present. In deciding which patients to screen, the rates provided above for the prevalence of *HLA- B*15:02* may offer a rough guide, keeping in mind the limitations of these figures due to wide variability in rates even within ethnic groups, the difficulty in ascertaining ethnic ancestry, and the likelihood of mixed ancestry. Carbamazepine should not be used in patients positive for *HLA-B*15:02* unless the benefits clearly outweigh the risks. Tested patients who are found to be negative for the allele are thought to have a low risk of SJS/TEN.

Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment. This information may be taken into consideration in determining the need for screening of genetically at-risk patients currently on carbamazepine.

The *HLA-B*15:02* allele has not been found to predict risk of less severe adverse cutaneous reactions from carbamazepine, such as maculopapular eruption (MPE) or to predict Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Limited evidence suggests that *HLA-B*15:02* may be a risk factor for the development of SJS/TEN in patients of Chinese ancestry taking other anti-epileptic drugs associated with SJS/TEN, including phenytoin. Consideration should be given to avoiding use of other drugs associated with SJS/TEN in *HLA-B*15:02* positive patients, when alternative therapies are otherwise equally acceptable.

Hypersensitivity Reactions and *HLA-A*31:01* Allele

Retrospective case-control studies in patients of European, Korean, and Japanese ancestry have found a moderate association between the risk of developing hypersensitivity reactions and the presence of *HLA-A*31:01*, an inherited allelic variant of the *HLA-A* gene, in patients using carbamazepine. These hypersensitivity reactions include SJS/TEN, maculopapular eruptions, and Drug Reaction with Eosinophilia and Systemic Symptoms.

*HLA-A*31:01* is expected to be present in the following approximate frequencies: greater than 15% in patients of Japanese and Native American ancestry; up to about 10% in patients of Han Chinese, Korean, European, and Latin American ancestry; and up to about 5% in African-Americans and patients of Indian, Thai, Taiwanese, and Chinese (Hong Kong) ancestry.

The risks and benefits of carbamazepine therapy should be weighed before considering carbamazepine in patients known to be positive for *HLA-A*31:01*.

General Information on *HLA* Genotyping and Hypersensitivity

Application of *HLA* genotyping as a screening tool has important limitations and must never substitute for appropriate clinical vigilance and patient management. Many *HLA-B*15:02*-positive and *HLA- A*31:01*-positive patients treated with carbamazepine will not develop SJS/TEN or other hypersensitivity reactions, and these reactions can still occur infrequently in *HLA-B*15:02*-negative and *HLA-A*31:01*-negative patients of any ethnicity. The role of other possible factors in the development of, and morbidity from, SJS/TEN and other hypersensitivity reactions, such as antiepileptic drug (AED) dose, compliance, concomitant medications, co-morbidities, and the level of dermatologic monitoring have not been studied.

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

2015 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

*HLA-B*15:02*: CARBAMAZEPINE

Patients with this genetic variation have a severely increased risk of experiencing the life-threatening cutaneous adverse event Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced SJS/TEN in these patients is 1.8-3.4%.

Recommendation:

1 choose an alternative if possible

*HLA-A*31:01*: CARBAMAZEPINE

Patients with this genetic variation have an increased risk of experiencing the life-threatening cutaneous adverse events DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced DRESS in these patients is 0.89%.

Recommendation:

1. carefully weigh the risk of DRESS and SJS/TEN against the benefits
2. if an alternative is an option, choose an alternative

*HLA-B*15:11*: CARBAMAZEPINE

Patients with this genetic variation have an increased risk of experiencing the life-threatening cutaneous adverse event Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN). The risk of carbamazepine-induced SJS/TEN in patients with the HLA-B*15:02 allele, which carries a 4.6-6.6 times higher risk than the HLA-B*15:11 allele, is 1.8-3.4%. This would equate to a risk of carbamazepine-induced SJS/TEN in these patients of 0.27-0.73%.

Recommendation:

1. carefully weigh the risk of SJS/TEN against the benefits
2. if an alternative is an option, choose an alternative

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

2017 Statement from the Clinical Pharmacogenetics Implementation Consortium (CPIC)

The therapeutic recommendations for *HLA-B*15:02* and carbamazepine remain unchanged from the original guideline (3) but in this update they are now also applicable to oxcarbazepine (4). These recommendations hold irrespective of the patient's region of origin or ethnic group. For patients who are *HLA-B*15:02* negative, carbamazepine or oxcarbazepine may be prescribed per standard guidelines. If a patient is carbamazepine-naïve or oxcarbazepine-naïve and *HLA-B*15:02* positive, carbamazepine and oxcarbazepine should be avoided, respectively, due to the greater risk of SJS/TEN. Other aromatic anticonvulsants, including eslicarbazepine, lamotrigine, phenytoin, fosphenytoin, and phenobarbital, have very limited evidence, if any, linking SJS/TEN with the *HLA-B*15:02* allele; however, caution should still be used when choosing an alternative agent. With regular dosing, carbamazepine- or oxcarbazepine-induced SJS/TEN usually develops within the first 4–28 days of therapy; therefore, patients who have been continuously taking carbamazepine or oxcarbazepine for longer than 3 months without developing cutaneous reactions are at extremely low risk (but not zero) of carbamazepine- or oxcarbazepine-induced adverse events in the future, regardless of *HLA-B*15:02* status.

For patients who are *HLA-A*31:01* negative, carbamazepine may be prescribed per standard guidelines (Table 3). If a carbamazepine-naïve patient also received testing for *HLA-B*15:02* and is positive for this allele, carbamazepine should be avoided regardless of the *HLA-A*31:01* genotype result. If a patient is carbamazepine-naïve and *HLA-A*31:01* positive, and if alternative agents are available, carbamazepine should be avoided due to the greater risk of SJS/TEN, DRESS, and MPE. Other aromatic anticonvulsants, including oxcarbazepine, have very limited evidence, if any, linking SJS/TEN, DRESS, and/or MPE with the *HLA-A*31:01* allele, and thus no recommendation can be made with respect to choosing another aromatic anticonvulsant as an alternative agent. If alternative agents are not available, consider the use of carbamazepine with increased frequency of clinical monitoring. Discontinue therapy at the first evidence of a cutaneous adverse reaction. As previously mentioned, since the latency period for cutaneous adverse drug reactions is known, if the patient is *HLA-A*31:01* positive and has previously used carbamazepine for longer than 3 months without incidence of a cutaneous adverse reaction, cautiously consider use of carbamazepine.

Please review the complete therapeutic recommendations that are located here: (4).

2014 Recommendations from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS)

Recommendation 1.1: Genetic testing for *HLA- B*15:02* is recommended for all carbamazepine (CBZ)-naive patients before initiation of carbamazepine 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 carbamazepine-naive patients before initiation of carbamazepine therapy (Level B – moderate in all patients; Table 6).

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

Recommendation 1.3: In patients who have previously experienced a hypersensitivity reaction (HSR) potentially related to carbamazepine, 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 antiepileptic drugs (AED) (oxcarbazepine, lamotrigine, phenytoin, phenobarbital, primidone).

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

Table 7. 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 (5).

Please review the complete therapeutic recommendations that are located here: (5).

Nomenclature

Nomenclature for selected HLA alleles

Allele name	dbSNP reference identifier for allele location	HGVS	IPD-IMGT/HLA
*HLA-B*15:02*	rs2844682 and rs3909184	NG_023187.1:c.[5T>G; 11T>C; 44C>G; 45G>A; 103T>G; 106G>A; 142T>G; 204A>G; 205G>A; 206A>T; 209A>C; 213G>C; 222G>A; 272A>C; 277G>A; 280C>A; 282G>C; 283G>A; 292G>T; 353C>T; 355C>A; 363C>G; 369C>T; 409C>T; 419A>C; 463C>A; 477C>G; 539G>T; 559G>C; 560A>T; 603C>G; 605A>C; 610G>C; 618T>G; 636C>T; 693T>C; 756T>C; 900G>A; 916G>A; 985G>A; 1008T>C; 1046G>C]	Allele Report for B*15:02:01 (HLA00165)

Nomenclature for selected continued from previous page.

Allele name	dbSNP reference identifier for allele location	HGVS	IPD-IMGT/HLA
*HLA-A*31:01*	rs1061235 and rs16333021	NM_002116.7:c.[41C>T; 97T>A; 98T>C; 238G>A; 243G>T; 282G>C; 290C>T; 363A>G; 413G>A; 448C>T; 502A>C; 524A>G; 527A>T; 555T>G; 633A>G; 642C>T; 649C>G; 651C>T; 652A>G; 691G>A; 808G>T; 829G>C; 870G>C; 899T>C; 945G>A; 952C>T; 964A>T; 967A>G; 987C>T; 992T>G; 1029T>C; 1033A>T; 1072G>A; 1077C>T]	Allele Report for A*31:01:02:01 (HLA00097)
*HLA-B*15:11*		NG_023187.1:c.[5T>G; 11T>C; 44C>G; 45G>A; 103T>G; 106G>A; 142T>G; 204A>G; 205G>A; 206A>T; 209A>C; 213G>C; 222G>A; 277G>A; 280C>A; 282G>C; 283G>A; 292G>T; 363C>G; 419A>C; 463C>A; 477C>G; 538C>T; 559G>C; 560A>T; 603C>G; 605A>C; 610G>C; 618T>G; 636C>T; 693T>C; 756T>C; 900G>A; 916G>A; 985G>A; 1008T>C; 1046G>C]	Allele Report for B*15:11:01 (HLA00174)

The IPD-IMGT/HLA Database includes the official sequences named by the WHO Nomenclature Committee for Factors of the HLA System. IPD: Immuno Polymorphism Database, IMGT: international ImMunoGeneTics project, HLA: Human Leucocyte Antigen. The sequence variation descriptions used by IMGT/HLA are in line with the HGVS recommendations for sequence variant descriptions.
Note: 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 (51).
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 (51). For *HLA-A*31:01*, rs1061235 is a tag SNP in Europeans (14) and rs16333021 is a tag SNP in Japanese (41). A study involving North American children of various ancestries showed that rs1061235 is not a suitable tag SNP in non-Caucasian individuals (42).
Guidelines on nomenclature of the HLA system are available from HLA Nomenclature.

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