Clinical Pharmacogenetics Implementation Consortium Guidelines for *HLA-B* Genotype and Carbamazepine Dosing

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Human leukocyte antigen B (*HLA-B*) is a gene that encodes a cell surface protein involved in presenting antigens to the immune system. The variant allele *HLA-B*15:02* is associated with an increased risk of Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in response to carbamazepine treatment. We summarize evidence from the published literature supporting this association and provide recommendations for the use of carbamazepine based on *HLA-B* genotype (also available on PharmGKB: http://www.pharmgkb.org). The purpose of this article is to provide information to allow the interpretation of clinical *HLA-B*15:02* genotype tests so that the results can be used to guide the use of carbamazepine. The guideline provides recommendations for the use of carbamazepine when *HLA-B*15:02* genotype results are available. Detailed guidelines regarding the selection of alternative therapies, the use of phenotypic tests, when to conduct genotype testing, and cost-effectiveness analyses are beyond the scope of this document. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines are published and updated periodically on the PharmGKB website at (http://www.pharmgkb.org).

FOCUSED LITERATURE REVIEW

A systematic literature review focused on *HLA-B*15:02* genotype and carbamazepine use (see **Supplementary Material** online) was conducted. Reviews were included to summarize much of the earlier literature.

GENE: *HLA-B*

Background

Human leukocyte antigen B (*HLA-B*) is a gene located on the short arm of chromosome 6 (6p21.3) that encodes a cell surface protein involved in presenting intracellular antigens to the immune system. These intracellular antigens are usually the normal breakdown products of intracellular proteins and are recognized as "self." However, if the antigen presented derives from a pathogen or, in some cases, a transplanted tissue, it may be recognized as "nonself" and trigger an immune response. *HLA-B* is part of a large cluster of genes known as the human major histocompatibility complex. The cluster contains three subgroups: classes I, II, and III. The *HLA-B* gene is a part of the class I complex, along with *HLA-A* and *HLA-C*.

Because HLA proteins present a wide variety of peptides for immune recognition, the *HLA* genes, and specifically *HLA-B*, are among the most highly polymorphic genes in the human genome. *HLA* polymorphisms were previously ascertained serologically, but newer approaches that exploit genotyping and DNA sequencing methods have revealed much greater complexity of genetic variation within this locus. For example, according to the World Health Organization Nomenclature Committee for Factors of the *HLA* System (http://hla.alleles.org), there are >2,000 identified *HLA-B* alleles, many of which differ from one another by more than one nucleotide. Each allele is designated by the gene name followed by an asterisk and a four- or six-digit identifier giving information about the allele type (designated by the first two digits) and specific protein subtypes (second set of digits). The allele type may correspond to the antigen detected by serological methods. Subtypes differ at one or more nucleotide positions that alter the protein-coding sequence. The details of HLA nomenclature have been described in a previous CPIC guideline.[1] The guidelines we present here specifically discuss only the *HLA-B*15:02* allele as it relates to carbamazepine-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), serious blistering cutaneous adverse drug reactions.

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Genetic test interpretation

Clinical genotyping tests exist for identifying *HLA-B* alleles, including *HLA-B*15:02*. The *HLA-B*15:02* allele predisposes to the development of carbamazepine-induced SJS/TEN but is not known to affect either carbamazepine pharmacokinetics or the development of other types of cutaneous adverse reactions (see below). Genotyping results are presented as "positive" if one or two copies of *HLA-B*15:02* are present or as "negative" if no copies of *HLA-B*15:02* are present. There is no intermediate genotype or phenotype. Phenotype assignments for *HLA-B*15:02* genotypes are summarized in **Table 1**.

Available genetic test options

Several methods of *HLA-B* genotyping are commercially available. The **Supplementary Material** online and http://www.pharmgkb.org contain more information on available clinical testing options.

Incidental findings

No other diseases have been linked to *HLA-B*15:02*. However, there have been reports linking the *HLA-B*15:02* allele to SJS/TEN from oxcarbazepine and phenytoin use, particularly in Asian populations.[2–8] Other *HLA-B* alleles are also associated with adverse reactions to drugs, such as the association between *HLA-B*57:01* and abacavir-induced hypersensitivity reaction,[9] and the association between *HLA-B*58:01* and increased risk of allopurinol-induced severe cutaneous adverse reactions (including but not limited to SJS/TEN).[10] CPIC guidelines are available for the latter two *HLA-B*–associated adverse drug reactions.[1,11]

Other considerations

*HLA-B*15:02* has a very distinct ethnic and regional distribution that is important to consider when evaluating population risk. Specifically, *HLA-B*15:02* is most prevalent in Oceanian, East Asian, and South/Central Asian populations (see **Supplementary Tables S1 and S2** online), ranging from 1 to >10% in some cases. The frequency of *HLA-B*15:02* is highest in Han Chinese, for which some estimates from the Yunnan province have been as high as 36%. In general, rates in China range from 1 to 12%. Rates in Singapore and Hong Kong have also been estimated at 10–12%. Rates in Malaysia and Thailand are estimated at 6–8%, whereas in different regions of India, the rates range from 2 to 6%. Korea and Japan have low frequencies of the allele at 0.5 and 0.1%, respectively. The allele is also quite rare in African populations (not observed) and Europeans (0–0.02%).

Carbamazepine can cause a wide variety of cutaneous adverse drug reactions, including mild maculopapular eruptions (MPEs), drug hypersensitivity syndrome, in which a cutaneous eruption is associated with systemic manifestations, and SJS/TEN,[12] the most severe manifestation. It is important to note that *HLA-B*15:02* is specific for SJS and TEN; there is no evidence that it predisposes to MPEs or hypersensitivity syndrome.[13] By contrast, another *HLA* allele, *HLA-A*31:01*, is associated with a wider range of carbamazepine hypersensitivity reactions, including MPEs, hypersensitivity syndrome, and SJS/TEN in both Caucasian and Japanese populations[13] (see **Supplementary Material** online for further discussion). These associations underscore the potential importance of other alleles in other populations with different clinical manifestations.[14,15]

DRUG: CARBAMAZEPINE

Background

Carbamazepine, an aromatic anticonvulsant related to the tricyclic antidepressants, is approved by the US Food and Drug Administration for the treatment of epilepsy and other seizure disorders, trigeminal neuralgia, and bipolar disorder. Carbamazepine reduces the propagation of abnormal impulses in the brain by producing a frequency- and voltage-dependent blockade of sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus.[16] Carbamazepine is commercially available as a regular-release or extended-release oral formulation, and therapy may be targeted by testing serum concentrations, with the traditionally accepted therapeutic range for treatment of epilepsy being 4–12 μg/ml.[17] Above this therapeutic range, adverse effects include diplopia, drowsiness, nausea, and sedation. Carbamazepine adverse effects that are not clearly dose or concentration dependent include aplastic anemia, hyponatremia, leucopenia, osteoporosis, and hypersensitivity reactions such as MPEs, hypersensitivity syndrome, SJS/TEN, or drug-induced liver injury. For additional information regarding the pharmacokinetics and pharmacogenomics of carbamazepine, refer to the PharmGKB website (http://www.pharmgkb.org/pathway/PA165817070).[18]

Approximately 10% of patients develop mild cutaneous adverse drug reactions, e.g. MPEs,[13] within the first 3 months of therapy.[19,20] *HLA-B*15:02* is specific for the carbamazepine-induced SJS and TEN. SJS is characterized by epidermal

Table 1 Assignment of likely HLA-B phenotypes based on genotypes

Genotype	Likely phenotype	Examples of diplotypes
Noncarrier of *HLA-B*15:02*. No **15:02* alleles reported, often reported as "negative" on a genotyping test.	Homozygous for an allele other than *15:02; at "normal" or reduced risk of carbamazepine-induced SJS/TEN	*X/*X[a]
Carrier of *HLA-B*15:02*. One or two**15:02* alleles, often reported as "positive" on a genotyping test.	Heterozygote or homozygous variant; at significantly increased risk of carbamazepine-induced SJS/TEN	*15:02/*X[a], *15:02/*15:02

See **Supplementary Material** online for estimates of genotype frequencies among different ethnic/geographic groups.

SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

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

detachment affecting up to 10% of body surface area, whereas TEN usually involves >30% of the body surface area. Patients with between 10 and 30% of the body surface area blistered are defined as having an overlap syndrome. Mortality rates are <5% for SJS and >30% for TEN, with sepsis being the most frequent cause of death.[21] An immune-mediated etiology has been shown for these reactions, which is consistent with the anamnestic response often seen clinically on drug rechallenge.[22] In terms of the immunopathology, cytotoxic T cells, or $CD8^+$ T cells (lymphocytes matured in the thymus that express the CD8 protein on their surface), are involved in SJS and TEN.[23,24]

Linking genetic variability to variability in drug-related-phenotypes

There is substantial evidence linking *HLA-B*15:02* genotype with the risk of SJS/TEN (see **Supplementary Table S3** online). Application of a grading system to evidence linking genotypic variability to phenotypic variability indicates a high quality of evidence in the majority of cases (**Supplementary Table S3**). The evidence presented here and in **Supplementary Table S3** provides the basis for the dosing recommendations in **Table 2**.

An increased risk of SJS/TEN has been associated with the *HLA-B*15:02* allele in Han Chinese and other Asian groups.[19,25,26] The genetic association of carbamazepine-induced SJS/TEN with *HLA-B*15:02* was first published by Chung *et al*. in 2004.[25] In this case–control analysis, 44 Han Chinese individuals with carbamazepine-induced SJS/TEN living in Taiwan were compared with 101 carbamazepine-tolerant and 93 randomly selected healthy individuals never exposed to the drug. All 44 cases (100%) were positive for the *HLA-B*15:02* allele, whereas only 3 (3%) carbamazepine-tolerant and 8 (8.6%) normal controls carried the allele. These results were replicated,[19] and a similar result was found in a Han Chinese population residing in Hong Kong.[26] The Food and Drug Administration issued a Health Alert in 2007 about changes to package labeling and recommendations for genetic testing in patients treated with carbamazepine.[27]

Consistent with the regional and ethnic distribution of the *HLA-B*15:02* allele, studies have shown the genetic risk of carbamazepine-associated SJS/TEN to be higher in several Asian countries, including Vietnam,[28] Cambodia,[28] the Reunion Islands,[28] Thailand,[5,29] some parts of India,[30] Malaysia,[31] and Hong Kong.[26] The *HLA-B*15:02* allele has not been observed in cases of SJS/TEN in various ancestral groups such as Japanese and Korean populations or non-Asian descendants in Europe or North America.[28,32–35] In the Han Chinese population, the sensitivity of *HLA-B*15:02* as a predictive test for SJS/TEN has been estimated at 98% and specificity has been estimated at 97%; the positive predictive value is estimated at 7.7% and the negative predictive value is estimated at 100%.[19] However, it is important to note that in one study, in a group of individuals thought to be of European origin, 4 of 12 individuals with SJS/TEN carried the *HLA-B*15:02* allele.[33] Subsequently, they were found to have some Asian ancestry. This example underscores the importance of considering the *HLA-B*15:02* allele carrier status regardless of self-reported ethnicity.

Therapeutic recommendations

Currently, the Food and Drug Administration recommends that "patients with ancestry in at-risk populations should be screened for the presence of *HLA-B*15:02* allele prior to starting carbamazepine" (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm). 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 (see **Supplementary Table S2** online for frequency information). 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 (summarized in **Supplementary Table S3** online) 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 2**).

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

Table 2 Carbamazepine therapy recommendations based on *HLA-B* genotype

Genotype	Phenotypic implications	Therapeutic recommendations	Classification of recommendations[a]
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[b]	Strong
		If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine	Optional

SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.

[a]Rating scheme described in the **Supplementary Material** online. [b]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 (see **Supplementary Material** online for details).

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.[36,37]

Recommendations for incidental findings

Several drugs structurally and therapeutically similar to carbamazepine have also been associated with SJS/TEN and *HLA-B*15:02*. The drug-specific evidence linking *HLA-B*15:02* and SJS/TEN is discussed in the **Supplementary Material** online and may have implications for choosing alternatives to carbamazepine in those who carry the *HLA-B*15:02* allele.

In one study, the *HLA-B*07:02* allele was absent in patients with carbamazepine-induced SJS/TEN but was present at frequencies of 18% in the control group and 14% in those with a mild hypersensitivity reaction, leading the authors to conclude that *HLA-B*07:02* may protect against carbamazepine-induced SJS/TEN. However, there is no course of action suggested based on this genotype.[32]

Other considerations

Not applicable.

Potential benefits and risks for the patient

A potential benefit of *HLA-B*15:02* testing is a significant reduction in the incidence of serious, sometimes fatal, SJS/TEN reactions to carbamazepine by identifying those who are at significant risk and recommending alternative treatments appropriate for the underlying indication. The success of *HLA-B*15:02* prospective screening in reducing the rate of SJS/TEN has recently been demonstrated clinically in a Chinese population.[38]

A potential risk of *HLA-B*15:02* testing is ruling out the use of carbamazepine in patients who may not have developed SJS/TEN; however, this risk is mitigated by the fact that there are often alternatives to carbamazepine with comparable effectiveness. Another potential risk would be an error in genotyping. In the event of a false-negative result, a high-risk patient could mistakenly be prescribed carbamazepine. However, because not all carbamazepine-induced SJS/TEN can be attributed to *HLA-B*15:02*, clinicians should carefully monitor all patients as standard practice. Genotype results are associated with a patient for a lifetime, and a genotyping error could have a broader impact on health care should other *HLA-B*15:02* associations be identified in the future.

Caveats: appropriate use and/or potential misuse of genetic tests

Recently, a systematic review by Yip *et al.* of the relationship between carbamazepine-induced SJS/TEN and *HLA-B*15:02* showed that the positive predictive value and negative predictive value for a screening test in Asians were 1.8% (7.7% in Han Chinese only) and 100%, respectively,[13,39] and that 461 patients would need to be tested to prevent one case of SJS/TEN. Furthermore, they determined that carriage of *HLA-B*15:02* in Asian patients was associated with a pooled odds ratio of 113.4 (95% confidence interval = 51.2–251.0; $P < 1 \times 10^{-5}$).[13] Therefore, a significant percentage of the patients carrying the allele would not suffer from carbamazepine-induced SJS/TEN, and it is not currently possible to distinguish these carriers. However, the benefit of the high negative predictive value is clinically relevant, where Asian non-carriers of the risk allele are virtually at no risk to develop SJS/TEN, based on the study of Yip *et al.*[13] Considering the severity of SJS/TEN, a negative test result will represent very valuable information when making treatment decisions related to carbamazepine. In the interest of patient safety, however, all patients should be monitored for cutaneous effects regardless of carrier status.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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CPIC guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time the guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variation among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC guidelines, or for any errors or omissions.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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