

# HLA-B\*15:02 Genotyping, Carbamazepine Hypersensitivity

Carbamazepine (CBZ) is an aromatic antiepileptic drug, approved for the treatment of epilepsy, bipolar disorder, and trigeminal neuralgia. Rarely, CBZ can induce severe, life-threatening reactions such as Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN), associated with very high morbidity and mortality (up to 10% for SJS, and up to 50% for TEN). In patients of Asian descent, CBZ-induced SJS/TEN is strongly associated with the presence of the HLA-B\*15:02 allele and occurs when activated immune cells contribute to the cellular death of keratinocytes in the skin, which causes epidermal destruction and detachment of the skin. Symptoms usually appear within the first months of treatment and include skin rash, hives, sores in the mouth, blistering or peeling of the skin, and erosion of the mucous membranes in the respiratory and gastrointestinal tract.<sup>1</sup>

## Disease Overview

### Incidence

SJS/TEN: 1-10/10,000 in countries with mainly White populations, but the risk in some Asian countries is estimated to be approximately 10 times higher<sup>2,3</sup>

Other CBZ-induced hypersensitivity reactions: ~5-10% of patients (most commonly mild cutaneous reactions such as MPE)

## Testing Strategy

- The FDA recommends that patients with ancestry in genetically at-risk populations (ie, in which HLA-B\*15:02 may be present) should be screened for the presence of HLA-B\*15:02 prior to initiating treatment with CBZ<sup>2,3</sup>
- Patients who test positive for HLA-B\*15:02 should not be treated with CBZ unless benefits clearly outweigh risk.<sup>2,3</sup>
- Not all patients carrying HLA-B\*15:02 have the risk of developing SJS or TEN; the majority (95-99%) tolerate CBZ.<sup>1</sup>

## Genetics

### Allele(s)

HLA-B\*15:02

Other members of the HLA-B75 serogroup detected by this assay can also be associated with CBZ-induced SJS/TEN, including HLA-B\*15:08, 15:11, 15:21, and possibly 15:31 and 15:32.

### Inheritance

Codominant

### Prevalence

The HLA-B\*15:02 allele is found almost exclusively in patients of Asian descent. Prevalence rates vary widely by country and ethnicity and may be difficult to assess, especially in patients with mixed ancestry.<sup>3</sup>

## Tests to Consider

### [HLA-B\\*15:02 Genotyping, Carbamazepine Hypersensitivity 2012049](#)

**Method:** Polymerase Chain Reaction/Sequence-Specific Oligonucleotide Probe Hybridization

- Identify patients prior to treatment with CBZ who may be at risk for developing SJS or TEN
- Patients negative for HLA-B\*15:02 have a low risk for developing SJS or TEN but not necessarily for other reactions (eg, maculopapular exanthema [MPE])

### Prevalence of HLA-B\*15:02 Allele in Ethnic Population Groups

Prevalence (%)	Ethnic Groups
>15	Hong Kong, Thailand, Malaysia, part of the Philippines

Prevalence (%)	Ethnic Groups
>5 positive	Chinese, Singapore, Taiwanese, Vietnamese, Filipino, Indian (Khandesh, West Bhili), Indonesian
1-5 positive	Chinese (Northern Han, Inner Mongolia)
0.1-1 positive	African American, Mexican, Japanese, Korean, Native American (Alaskan Yupik)
<0.1 positive	White, Hispanic, African, Chinese (Tibetan), Omani

## Test Interpretation

### Clinical Sensitivity/Specificity

- Sensitivity: 80-97% among populations in which HLA-B\*15:02 is common
- Specificity: 99% among populations in which HLA-B\*15:02 is common

Test has a low positive predictive value for SJS/TEN (1-5%) but a high negative predictive value. Within the Chinese population (of Han descent), absence of the HLA-B\*15:02 allele has 100% negative predictive value for SJS/TEN.

### Analytic Sensitivity/Specificity

>99%

## Results

Result	Variant(s) Detected	Clinical Significance	Treatment
Positive	HLA-B*15:02 heterozygous or homozygous detected	Predicts significantly increased risk for CBZ-induced SJS/TEN in individuals of Asian ancestry	Avoidance of CBZ therapy is recommended Alternative medication should be used, avoiding structurally similar aromatic antiepileptic drugs (eg, oxcarbazepine, phenytoin, fosphenytoin, lamotrigine)
Negative	HLA-B*15:02 not detected	Predicts no risk for CBZ-induced SJS/TEN in individuals of Asian ancestry	CBZ can be used as first-line therapy

## Limitations

- A negative result for HLA-B\*15:02 does not replace the need for therapeutic drug or other clinical monitoring.
- Copy number of HLA-B\*15:02 will not be reported.
- The absence of the risk allele does not exclude development of other types of CBZ hypersensitivity, such as CBZ-induced MPE or hypersensitivity syndrome (HSS).
- Other genetic or nongenetic factors that may affect hypersensitivity to CBZ are not identified.
- The HLA-A\*31:01 allele, which may be moderately associated with SJS/TEN in patients with European, Native American, Korean, and Japanese ancestry, is not identified by this test.
- Rare, undocumented alleles may occur that may or may not give false-positive results.
- CBZ therapy should be discontinued in all individuals if symptoms of SJS or TEN develop, regardless of HLA-B\*15:02 status.

## References

1. Dean L. [Carbamazepine therapy and HLA genotype](#). In: Pratt VM, Scott SA, Pirmohamed M, et al, editors. Medical Genetics Summaries. National Center for Biotechnology Information; 2012. [Updated: Aug 2018; Accessed: Aug 2022].
2. National Institutes of Health, DailyMed. [Carbamazepine drug label](#). [Updated: Jan 2022; Accessed: Aug 2022]
3. U.S. Food and Drug Administration, Drugs@FDA: FDA-approved drugs. [Tegretol](#). Novartis [Updated: Feb 2009; Accessed: Aug 2022]

## Related Information

[HLA Testing](#)

