HLA-B*15:02 Genotyping, Carbamazepine Hypersensitivity

Last Literature Review: August 2022 Last Update: May 2024

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.[1]

Featured ARUP Testing

HLA-B*15:02 Genotyping, Carbamazepine Hypersensitivity 2012049

Method: Polymerase Chain Reaction (PCR)
Sequence-Specific Oligonucleotide Probe Hybridization
Massively Parallel Sequencing

- 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])

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[2,3]

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.[2,3]
- Patients who test positive for HLA-B*15:02 should not be treated with CBZ unless benefits clearly outweigh risk.[2,3]
- Not all patients carrying HLA-B*15:02 have the risk of developing SJS or TEN; the majority (95-99%) tolerate CBZ.[1]

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.

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.[3]

Prevalence of HLA-B*15:02 Allele in Ethnic Population Groups	
Prevalence (%)	Ethnic Groups
>15	Hong Kongese, Malaysian, some groups in the Philippines, and Thai
>5 positive	Chinese, Singaporean, Taiwanese, Vietnamese, Filipino, Indian (Khandesh, West Bhili), Indonesian
1-5 positive	Chinese (Northern Han, Inner Mongolian)
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.
- The 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, eds. *Medical Genetics Summaries*. National Center for Biotechnology Information. 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. Tegretol. Novartis. Updated Feb 2009; accessed Aug 2022.

Related Information

HLA Testing

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