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.¹

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 higher²,³

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

<table>
<thead>
<tr>
<th>Prevalence (%)</th>
<th>Ethnic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15</td>
<td>Hong Kongese, Malaysian, some groups in the Philippines, and Thai</td>
</tr>
<tr>
<td>&gt;5 positive</td>
<td>Chinese, Singaporean, Taiwanese, Vietnamese, Filipino, Indian (Khandesh, West Bhili), Indonesian</td>
</tr>
<tr>
<td>1-5 positive</td>
<td>Chinese (Northern Han, Inner Mongolian)</td>
</tr>
<tr>
<td>0.1-1 positive</td>
<td>African American, Mexican, Japanese, Korean, Native American (Alaskan Yupik)</td>
</tr>
<tr>
<td>&lt;0.1 positive</td>
<td>White, Hispanic, African, Chinese (Tibetan), Omani</td>
</tr>
</tbody>
</table>

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

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

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


Related Information

HLA Testing