HLA-B*15:02 Genotyping, Carbamazepine Hypersensitivity

Indications for Ordering

- Identify patients prior to treatment with carbamazepine (CBZ) who may be at risk for developing Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- Genetically high-risk populations include those in which HLA-B*15:02 is common – predominantly Asian ancestry
- Recommended for patients not currently taking carbamazepine

Test Description

- Polymerase chain reaction
- Sequence-specific oligonucleotide probe hybridization

Tests to Consider

Primary test

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- Identifies individuals at risk for CBZ-induced SJS/TEN

Disease Overview

Incidence

- SJS and TEN are rare – 1-10/10,000
- CBZ-induced hypersensitivity reactions occur in ~5-10% of patients
  - Most commonly includes mild cutaneous reactions (eg, maculopapular exanthema [MPE])

Prevalence of HLA-B*15:02 Allele in Ethnic Population Groups	
>5% positive	Chinese, Singapore, Taiwanese, Hong Kong, Thai, Malaysian, 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	Caucasian, Hispanic, African, Chinese (Tibetan), Omani

Symptoms

- Typically occur 1-3 weeks after initiation of CBZ treatment
- Caused by immune-mediated keratinocyte cell death that leads to skin detachment
  - <10% of body surface involved in SJS
  - Usually >30% of body surface involved in TEN
  - Associated with high morbidity and mortality
    - Up to 10% for SJS
    - Up to 50% for TEN
- SJS
  - Milder form of TEN
  - Upper respiratory tract-like symptoms
    - Fever (85% of cases), sore throat, headache, chills, cough with thick purulent sputum
    - Arthralgia
  - Mucocutaneous lesions
    - Nonpruritic
    - Last 2-4 weeks
  - Burning rash beginning symmetrically on face and upper torso
    - Lesions may involve esophagus, pharynx, larynx, anus, trachea, vagina, urethra
  - Ocular symptoms
    - Burning sensation, photophobia, dry eyes, itching
- TEN
  - Potentially life threatening
  - Widespread erythema, necrosis, bullous detachment of epidermis and mucous membranes
  - Gastrointestinal hemorrhage, respiratory failure, genitourinary and ocular complications
    - Can lead to sepsis and/or death

Screening/detection

- CBZ belongs to the class of aromatic antiepileptic drugs
  - Approved for treatment of epilepsy and trigeminal neuralgia
- FDA recommendations
  - HLA-B*15:02 testing should be performed in patients with ancestry in populations in which HLA-B*15:02 may be present prior to initiating CBZ therapy
    - Patients positive for HLA-B*15:02 should not be treated with CBZ unless benefits clearly outweigh risk
- Not all patients carrying HLA-B*15:02 have risk of developing SJS or TEN
  - Majority (95-99%) tolerate CBZ
- Patients negative for HLA-B*15:02
  - Low risk for developing SJS or TEN, but not necessarily for other side effects
    - MPE
    - Hypersensitivity syndrome (HSS)

Genetics

Gene – HLA-B*15:02

Inheritance – codominant

Test Interpretation

Sensitivity/specificity

- Clinical sensitivity/specificity – 80-97% and 99%, respectively, in populations where risk allele is common
  - Low positive predictive value for SJS/TEN (1-5%)
  - High negative predictive value
  - Within Chinese Han population, absence of B*15:02 allele has 100% negative predictive value for SJS/TEN
- Analytical sensitivity/specificity – >99%

Results

- 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
      - 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

- Negative result for HLA-B*15:02 does not replace the need for therapeutic drug or other clinical monitoring
- Absence of risk allele does not exclude development of other types of CBZ hypersensitivity, such as CBZ-induced MPE or HSS
- Other genetic or nongenetic factors that may affect hypersensitivity to CBZ are not identified
- 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