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

HLA-B*15:02 Genotyping, Carbamazepine Hypersensitivity

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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 (e.g. maculopapular exanthema [MPE])
  - 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
  o Low positive predictive value for SJS/TEN (1-5%)
  o High negative predictive value
  o Within Chinese Han population, absence of B*15:02 allele has 100% negative predictive value for SJS/TEN
• Analytical sensitivity/specificity: >99%

Results
• Positive
  o 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
  o 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