HLA-B*1502 Variant Analysis for Carbamazepine and Oxcarbazepine Response

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is HLA-B*1502

Definition

Variation in the HLA-B gene is associated with increased risk for adverse reactions to certain drugs. Testing positive for either one or two HLA-B*1502 alleles increases a person's risk for a serious adverse skin reaction to carbamazepine.\(^1,2\)

- Carbamazepine (Tegretol\(^\text{®}\), Tegretol XR\(^\text{®}\), Equetro\(^\text{®}\), Epitol\(^\text{®}\), Carbatrol\(^\text{®}\)) is an antiepileptic agent used in the treatment of seizure disorders, psychiatric disorders, and pain from trigeminal neuralgia.
- Oxcarbazepine (Oxtellar XR\(^\text{®}\)) is the keto-analog to carbamazepine and shares many therapeutic indications with carbamazepine, and adverse effects.
- A strong association between the risk of developing Stevens-Johnson syndrome (SJS) and/or toxic epidermal necrolysis (TEN) with carbamazepine and oxcarbazepine treatment and the presence of the inherited variant of the HLA-B gene, HLA-B*1502, has been demonstrated in studies involving patients of Chinese ancestry. For this population, the risk of having a serious reaction is 10 times higher than the risk in Caucasians for which 1 to 6 per 10,000 new users of carbamazepine have a serious reaction to the drug.\(^2-8\)
- Across Asian populations, notable variation exists in the prevalence of HLA-B*1502. Individuals at highest risk are those of Han Chinese descent, followed by those in Vietnam, Cambodia, the Reunion Islands, Thailand, India (specifically Hindus), Malaysia, and Hong Kong. The frequency of HLA-B*15:02 is very low in other populations.\(^1\)
• Testing for HLA-B*1502 should be performed prior to initiating carbamazepine treatment for most patients of Asian ancestry. Over 90% of carbamazepine treated patients who will experience SJS/TEN have this reaction within the first few months of treatment and providers should consider this in determining the need for screening at-risk patients who are currently on therapy.¹

• Having HLA-B*1502 is not abnormal, and there is no other known risk from having it.¹

**Test information**

• HLA-B*1502 testing is performed using DNA extracted from whole blood or cheek cells. The test is positive if either one or two HLA-B*1502 alleles are detected and negative if no HLA-B*1502 alleles are detected.²

**Guidelines and evidence**

• The Clinical Pharmacogenetic Implementation Consortium (2013) published guidelines on the use of HLA-B*1502 testing for patients prescribed carbamazepine¹ An update was published in 2017 with the scope of recommendations expanded to include guidance on the use of oxcarbazepine.⁹
  
  o “HLA-B*1502 has a very distinct ethnic and regional distribution that is important to consider when evaluating population risk...The frequency of HLA-B*1502 is highest in Han Chinese...estimates...have been as high as 36%. In general, rates in China range from 1 to 12%. Rates in Singapore and Hong Kong have also been estimated at 10–12%. Rates in Malaysia and Thailand are estimated at 6–8%, whereas in different regions of India, the rates range from 2 to 6%. Korea and Japan have low frequencies of the allele at 0.5 and 0.1%, respectively. The allele is also quite rare in African populations (not observed) and Europeans (0–0.02%).”

  o “HLA-B*1502 is specific for SJS and TEN; there is no evidence that it predisposes to MPEs or hypersensitivity syndrome.”

  o “Much of the evidence linking HLA-B*1502 to SJS/TEN was generated in both children and adults.”

  o “Carbamazepine-induced and oxcarbazepine-induced SJS/TEN usually develops within the first 3 months of therapy; therefore, patients who have been taking carbamazepine or oxcarbazepine for longer than 3 months without developing cutaneous reactions are at low risk (but not zero) of carbamazepine-induced adverse events in the future, regardless of HLA-B*1502 status.”

• A very early study has demonstrated a potential relationship between two other members of the HLA-B75 serotype commonly found in Southeast Asian populations and carbamazepine-induced SJS/TEN. There was a significant association with SJS/TEN found for Southeast Asian individuals with HLA-B*1521 and HLA-B*1511.
who were prescribed carbamazepine. It was discovered that all HLA-B75 serotype molecules shared a similar capability to bind carbamazepine. More studies must be performed to further delineate this association.\textsuperscript{8}

- A systematic review and meta-analysis of associations between HLA genotypes and oxcarbazepine-induced cutaneous adverse drug reactions (OXC-cADRs), including Stevens-Johnson syndrome (SJS) and maculopapular rash, was completed and found strong associations between the HLA-B*1502 and OXC-cADRs (SJS and maculopapular rash) in both controls from general population and OXC-tolerant groups. The authors conclude that for patient safety, genetic screening especially for HLA-B*1502 prior to OXC therapy at least in these closely related ethnicities is warranted.\textsuperscript{10}

- Product labeling for carbamazepine (Tegretol XR\textsuperscript{®} ) warns for the potential of developing a serious dermatological reaction from treatment with carbamazepine in HLA-B*1502 positive individuals.\textsuperscript{1}
  
  o Carbamazepine should not be used in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks. Patients who test negative for the allele have a low risk of SJS/TEN, but should have routine monitoring for toxicity.\textsuperscript{1}
  
  o Carbamazepine should be discontinued at the first sign of a rash, unless the rash is clearly not drug-related. If signs or symptoms suggest SJS/TEN, carbamazepine should not be resumed and alternative therapy should be considered.\textsuperscript{1}

- Product labeling for for oxcarbazepine states that, “testing for the presence of the HLA-B*1502 allele should be considered in patients with ancestry in genetically at-risk populations prior to initiating treatment with the drug, due to the risk for Stevens-Johnson syndrome or toxic epidermal necrolysis.” \textsuperscript{11}
  
  o “The use of oxcarbazepine should be avoided in patients positive for HLA-B*1502 unless the benefits clearly outweigh the risks.” \textsuperscript{11}
  
  o “Consideration should also be given to avoid the use of other drugs associated with SJS/TEN in HLA-B*1502 positive patients, when alternative therapies are otherwise equally available.” \textsuperscript{11}

**Criteria**

HLA-B*1502 variant testing is indicated in individuals with Asian ancestry prior to initiation of or during the first nine months of treatment with carbamazepine or oxcarbazepine therapy.
References