

HLA-B*5701 Associated Variant Genotyping for Abacavir Hypersensitivity

*ASSESSES THE PRESENCE OF A GENETIC VARIANT ASSOCIATED WITH THE HLA-B*5701 ALLELE TO IDENTIFY INDIVIDUALS AT RISK FOR ABACAVIR HYPERSENSITIVITY REACTION*

Disease Overview

- Abacavir sulfate (Ziagen[®]) is a nucleoside reverse transcriptase inhibitor (NRTI) used in combination with other antivirals in the treatment of HIV infection.
- During the first six weeks of treatment approximately 5–8 percent of Caucasians and 2–3 percent of African-Americans develop serious and sometimes fatal abacavir hypersensitivity reaction (ABC HSR).
 - ABC HSR is often associated with two or more of the following symptoms: fever, rash, malaise/fatigue, respiratory symptoms, and gastrointestinal symptoms (nausea, vomiting, and diarrhea). Symptoms typically appear suddenly and worsen with each subsequent abacavir dose. Upon discontinuation of abacavir, symptoms improve within 48–72 hours.
 - Administration of abacavir following ABC HSR is contraindicated as it can lead to a more severe reaction.
- Hypersensitivity to abacavir has been strongly associated with the major histocompatibility complex class I human leukocyte antigen (HLA), specifically the HLA-B*5701 allele.
- DNA-based testing to assess the presence of HLA-B*5701 offers higher specificity than serological testing because monoclonal antibodies may show cross reactivity with other HLA subtypes.
- In 2008, the FDA recommended pre-therapeutic screening for the HLA-B*5701 allele and that patients testing positive should not be treated with a regimen containing abacavir. Routine screening has been shown to reduce the incidence of ABC HSR from 8 percent to less than 0.5 percent in abacavir naïve patients.

Epidemiology

The prevalence of the HLA-B*5701 allele varies by ethnicity: Indian: 0.20; Thai: 0.11; Caucasian: 0.08; African-American 0.02; Asian: rare.

Genetics

- Co-dominant inheritance.
- Penetrance is 98 percent. Approximately 2 percent of individuals who are HLA-B*5701-positive are tolerant to abacavir. This finding demonstrates that the HLA-B*5701 status is necessary, but not sufficient by itself, for manifestation of ABC HSR.

- The HLA-B*5701 allele is in linkage disequilibrium ($r^2=1.0$) with the single-nucleotide polymorphism (SNP) rs2395029 in the *HCP5* gene; therefore, detection of *HCP5* rs2395029 predicts the presence of HLA-B*5701.
- The *HCP5* (HLA complex P5) gene is located 100 kb centromeric from HLA-B on chromosome 6. The SNP rs2395029 represents a missense change of T>G (valine to glycine).

Indications for Ordering

- Pre-therapeutic identification of individuals who should avoid abacavir.
- Screening of individuals, prior to reinitiation, who have previously tolerated abacavir but whose HLA-B*5701 status is unknown.

Interpretation

- Testing for a genetic variant associated with ABC HSR does not replace the need for therapeutic drug or other clinical monitoring.
- HLA-B*5701 negative: predicts no increased risk for abacavir hypersensitivity.
- HLA-B*5701 heterozygous or homozygous: predicts a significantly increased risk for abacavir hypersensitivity; avoidance or discontinuation of abacavir is advised.

Methodology

- Polymerase chain reaction (PCR) and fluorescence monitoring to detect the SNP rs2395029, which is in linkage disequilibrium with HLA-B*5701.
- Clinical sensitivity and specificity for immunologically confirmed ABC HSR are 98 and 99 percent, respectively.
- Analytical sensitivity and specificity for prediction of HLA-B*5701 carrier status by SNP rs2395029 genotyping are 99 percent.

Limitations

- Rare diagnostic errors may occur due to primer-site mutations.
- Rare recombination events between *HCP5* SNP rs2395029 and HLA-B*5701 may occur.
- Non-genetic factors that may affect drug sensitivity are not identified.

References

1. Colombo S, et al. The HCP5 single-nucleotide polymorphism: a simple screening tool for prediction of hypersensitivity to abacavir. *J Infect Dis* 2008;198(9):864–7.
2. Hughes CA, et al. Abacavir hypersensitivity reaction: an update. *Ann Pharmacother* 2008;42:387–96.
3. Mallal S, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358:568–79.
4. Saag M, et al. High sensitivity of human leukocyte antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis* 2008;46(7):1111–8.

Test Information

2002429

HLA-B*5701 Associated Variant Genotyping for Abacavir Hypersensitivity

For specific collection, transport, and testing information, refer to the ARUP website at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.

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