HLA-B*58:01 Genotyping, Allopurinol Hypersensitivity

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HLA-B*58:01 genotyping can be used to identify patients who are at increased risk for developing severe cutaneous adverse reactions (SCAR) after treatment with allopurinol, based on the presence of the HLA-B*58:01 allele. SCAR, also known as allopurinol hypersensitivity reaction, includes Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

Featured ARUP Testing

HLA-B*58:01 Genotyping, Allopurinol Hypersensitivity 3001393

Method: Polymerase Chain Reaction/Sequence-Specific Oligonucleotide Probe Hybridization

Disease Overview

The presence of the HLA-B*58:01 allele shows strong association with allopurinol-induced SCAR, including SJS and TEN.

Prevalence and/or Incidence

HLA-B*58:01 allele frequency varies by ethnicity. The highest frequencies are found in Asian populations: up to 20% in Taiwan, Singapore, and among Han Chinese; 15.4% in India; 14.2% in Hong Kong; 12% in China and Korea; and 11% in Indonesia.

HLA-B*58:01 Allele Frequency in U.S. Population

Ethnicity	Allele Frequency (%)
Asians	5.3
African Americans	3.8
Native Hawaiians or Pacific Islanders	1.45
Hispanics	1.35
American Indians or Alaska Natives	1.19
Whites	0.8

Symptoms

- Allopurinol is a major cause of SCAR, with an estimated risk of 0.1-0.4%.
- SCAR is manifested by SJS, TEN, or a drug reaction with eosinophilia, and systemic symptoms.
- Symptoms include rash combined with eosinophilia, leukocytosis, fever, hepatitis, and progressive kidney failure.
- Allopurinol-induced SCAR typically develops within weeks or a few months after initiation of treatment, and can be serious, with up to 25% mortality.

Diagnostic Issues

- In addition to SCAR, a mild skin rash not associated with systemic symptoms or organ damage may develop in patients taking allopurinol.
  - These less severe rashes may occur in 2-3% of patients, and cannot be predicted by HLA-B*58:01 allele status.
- FDA guidelines recommend discontinuing allopurinol if a rash develops, regardless of allele status.

Screening/Detection

- Allopurinol is the most commonly used drug to treat hyperuricemia and gout. It inhibits xanthine oxidase, a key enzyme involved in uric acid formation.
- Due to the severity of allopurinol-induced SCAR, guidelines from the Clinical Pharmacogenomics Implementation Consortium (CPIC) recommend testing for the HLA-B*58:01 allele prior to initiation of therapy.

Genetics

Gene

HLA-B*58:01 allele

Inheritance

Codominant

Structure/Function

- The HLA-B*58:01 allele is located in the Class I HLA region, on human chromosome 6 (6p21.1-6p21.3).
- HLA-B58 encoded by the HLA-B*58:01 allele is expressed on the surface of all nucleated cells and has important immunological role in antigen presentation to T lymphocytes.

Test Interpretation

Sensitivity/Specificity

- Overall 50-60% sensitivity and ~90% specificity in pooled populations.
  - Higher in populations with increased HLA-B*58:01 allele frequency
    - 90-100% sensitivity in Korean, Thai, Sardinia Italian, and Han Chinese populations.
- Low positive-predictive value (~1.5%), and high negative-predictive value for the HLA-B*58:01 allele, especially in patients of Asian descent (>99%).
- Analytical sensitivity/specificity is >99%.

Results

Positive

- HLA-B*58:01, heterozygous or homozygous, is detected.
- The presence of this allele increases risk for allopurinol-induced SCAR, including SJS or TEN.
  - Allopurinol treatment is contraindicated.
  - Alternative medication should be used as first-line therapy.
- Therapy should be discontinued immediately if symptoms of SJS or TEN develop.

Negative

- HLA-B*58:01 is not detected.
- The patient is not at risk for allopurinol-induced SCAR, including SJS or TEN.
  - Allopurinol can be used per standard dosing guidelines.
- Testing negative for HLA-B*58:01 does not totally eliminate the possibility of developing SCAR, especially in the White population with low-risk allele frequency.
- Allopurinol therapy should be discontinued in all patients if symptoms of SJS or TEN develop, regardless of HLA-B*58:01 status.

Limitations

- Copy number of HLA-B*58:01 will not be reported.
- Negative result for HLA-B*58:01 does not replace the need for therapeutic drug monitoring or other clinical testing.
- Other genetic and nongenetic factors that influence allopurinol-related adverse reactions are not evaluated.
- Diagnostic errors can occur due to rare sequence variations, or the presence of rare and undocumented alleles.

Additional Resources

Yu KH, Yu CY, Fang YF. Diagnostic utility of HLA-B*5801 screening in severe allopurinol hypersensitivity syndrome: an updated systematic review and meta-analysis. *Int J Rheum Dis*. 2017;20(9):1057-1071.

Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther*. 2013;93(2):153-158.

Saito Y, Stamp LK, Caudle KE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for human leukocyte antigen B (HLA-B) genotype and allopurinol dosing: 2015 update. *Clin Pharmacol Ther*. 2016;99(1):36-37.

Related Information

Gout

ARUP Laboratories is a nonprofit enterprise of the University of Utah and its Department of Pathology. 500 Chipeta Way, Salt Lake City, UT 84108
(800) 522-2787 | (801) 583-2787 | aruplab.com | arupconsult.com