*HLA-B*58:01* Typing

Test Code: 93932 (X)

Specimen Requirements: 5 mL room-temperature whole blood (yellow- or lavender-top tube); 3 mL minimum

CPT Code*: 81381

CLINICAL USE

- Evaluate risk of severe cutaneous adverse reactions (SCARs) to allopurinol

CLINICAL BACKGROUND

Allopurinol, a xanthine oxidase inhibitor, is widely used to treat conditions associated with hyperuricemia such as uric acid kidney stones, uric acid nephropathy during chemotherapy (tumor lysis syndrome), and gout.[1] However, allopurinol is a frequent cause of adverse drug reactions, including SCARs.[1] These reactions are particularly problematic given the rising prevalence of gout in the United States and other countries, which is driven by increased frequencies of conditions that promote hyperuricemia.[2] These conditions include hypertension, obesity, metabolic syndrome, type 2 diabetes, and chronic kidney disease (CKD), in which the increase in the uric acid concentration is proportional to the decrease in glomerular filtration rate.[2-4]

SCARs include drug hypersensitivity syndrome (DHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).[1] The spectrum of DHS, SJS, and TEN in response to allopurinol is frequently referred to as allopurinol hypersensitivity syndrome (AHS) and is estimated to occur in 1 of 1,000 allopurinol users in the United States.[4] AHS is associated with marked morbidity and a mortality rate of 20% to 25%.[4] Until recently, there was no way of predicting which patients were likely to develop AHS.

Human leukocyte antigen (HLA)-B alleles have been shown to be predictive of drug-induced adverse reactions.[1] An early study of Han Chinese found the *HLA-B*58:01* allele to be present in 100% of patients with allopurinol-induced SCARs, but in only 15% of allopurinol-tolerant controls.[5] Subsequent studies confirmed the association between *HLA-B*58:01* and allopurinol-induced SCARs in Japanese, Korean, Thai, and European individuals. The odds of an adverse reaction were 29- to 580-fold greater for individuals with an *HLA-B*58:01* allele than for those without, with odds being highest for Han Chinese and Thai populations.[1] Similar to risk odds, *HLA-B*58:01* allele frequencies vary by race or ethnicity; they are highest in Han Chinese, Thai, and Korean populations and lower in European and Japanese populations (**Table**).[4,6,7]

Risk levels and allele frequencies are factored into guidelines for gout management and for allopurinol. The American College of Rheumatology guidelines recommend consideration of *HLA-B*58:01* genotyping before allopurinol therapy in populations with a high *HLA-B*58:01* allele frequency and at high risk for AHS (eg, all patients of Han Chinese or Thai descent and Koreans with stage 3 or worse CKD).[4] The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines note that *HLA-B*58:01* has a high negative predictive value, particularly in Asian patients; thus, testing for the allele could reduce the risk of SCARs. The CPIC guidelines also recommend against the use of allopurinol in *HLA-B*58:01* carriers and recommend consideration of an alternative therapy in these patients.[1]

The Quest Diagnostics *HLA-B*58:01* Typing assay determines the presence of the *HLA-B*58:01* allele and thus identifies patients at increased risk of allopurinol-induced SCARs.

Table. Allele Frequencies by Race or Ethnicity[4,6,7]

Race or Ethnicity	Allele Frequency, %
Asian	5.3
Korean	~12
Thai	8.6
Han Chinese	7.3
Japanese	0.6
African American or Black	3.9
Native Hawaiian or Pacific Islander	1.5
Hispanic or Latino	1.4
Native American	1.2
White	0.8

INDIVIDUALS SUITABLE FOR TESTING

- Individuals receiving or being considered for allopurinol therapy

METHOD

An *HLA-B*58* allele is screened by amplification of the selected region of the *HLA-B* locus by a laboratory developed test (LDT) that uses real time PCR.

If an *HLA-B*58* allele is detected, *HLA-B*58:01* status is determined using an FDA-approved *HLA-B* genotyping kit.

REFERENCE RANGES

*HLA-B*58:01* not detected

INTERPRETIVE INFORMATION

Presence of the *HLA-B*58:01* allele is associated with an increased risk of allopurinol-induced SCARs. Allopurinol should not be used[1] or should only be used with caution[4] in these patients.

Absence of *HLA-B*58:01* indicates decreased risk of SCARs but does not indicate protection from reactions to allopurinol.

References

1. 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;93:153-158.
2. Prasad Sah OS, Qing YX. Associations between hyperuricemia and chronic kidney disease: a review. *Nephrourol Mon.* 2015;7:e27233.
3. Jung JW, Song WJ, Kim YS, et al. *HLA-B58* can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol Dial Transplant.* 2011;26:3567-3572.
4. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken).* 2012;64:1431-1446.
5. Hung SI, Chung WH, Liou LB, et al. *HLA-B*5801* allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A.* 2005;102:4134-4139.
6. 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;99:36-37.
7. Tassaneeyakul W, Jantararoungtong T, Chen P, et al. Strong association between *HLA-B*5801* and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenet Genomics*. 2009;19:704-709.

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This test was developed and its performance characteristics determined by Quest Diagnostics Nichols Institute. It has not been cleared or approved by the US Food and Drug Administration, as the FDA has determined that such clearance or approval is not necessary. Performance characteristics refer to the analytical performance of the test.