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Is HLA B genotyping the future of gout pharmacogenomics?

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Abstract

Advances in pharmacogenomics have improved understanding of allopurinol hypersensitivity syndrome (AHS), and new research suggests HLA-B*5801 is a strong risk factor for this condition; in some populations, almost all patients who develop AHS carry this allele. This discovery could influence the treatment of gout, in particular, how allopurinol is used.

Keywords

Allopurinol; HLA-B*58:01; allopurinol hypersensitivity syndrome; severe cutaneous adverse reactions; adverse events; side effects; hypersensitivity reaction; Stevens-Johnson syndrome; toxic epidermal necrolysis; TEN; SJS; complications

Allopurinol is the most commonly used medication for the treatment of hyperuricemia in patients with gout. Allopurinol hypersensitivity syndrome (AHS) is rare but an important complication of allopurinol therapy, given that the associated mortality rate can be as high as 20–30%. Although the incidence of AHS is unknown, prevalence has been estimated as between 0.1–0.4%.¹ AHS is a type of severe cutaneous adverse reactions (SCARs) which manifest as drug-induced hypersensitivity syndromes (such as AHS). Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN). Indeed allopurinol has also been shown to be one of most frequent causes of SJS and TEN.² AHS SCARs can present skin rash, fever, hepatitis and acute renal failure, and patients with this condition could also have leukocytosis and/or eosinophilia.³ Recently, Hershfield *et al.*⁴ presented clinical recommendations for the management of gout that highlighted the role of the HLA-B*5801 allele in the occurrence of AHS. Recognition of the association between HLA-B*5801 and AHS could advance gout pharmacogenomics and improve prediction of allopurinol hypersensitivity, thus increasing the safety of profile of this effective therapeutic.

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The systematic literature review conducted by Hershfield *et al.*⁴ identified pharmacogenetic information on the association of HLAB*58:01 allele with allopurinol-induced SCARs, updating a meta-analysis conducted previously by Zineh and colleagues.⁵ Hershfield *et al.*⁴ summarized studies that reported strong positive association of HLA-B*5801 with allopurinol-associated SCAR in various populations, including one study each in Han Chinese, Thai, Japanese, Korean and European populations.⁴ Each study included in the analysis used a population control group and two studies also included an allopurinol-tolerant control group (Han Chinese and Korean).⁴ According to Hershfield and colleagues⁴ the estimated HLA-B*5801 allele carrier frequency in major racial and ethnic groups is 6.1% in Asian populations, 4.3% in black people, 0.75% in white people, 1.2% in Hispanic individuals and 3.7% in Middle Eastern groups.⁴ In addition, the previously mentioned meta-analysis had provided odds ratios for allopurinol-induced SCARs in HLA-B*5801 carriers with a pooled odds ratio of 90 (95% CI 36–231) compared with all controls (healthy controls and allopurinol-tolerant controls).⁵ On the basis of the pharmacogenetic data analysed, Hershfield and co-workers⁴ provided recommendations for the clinical use of allopurinol in individuals who have undergone HLA-B*5801 genotyping.

Current guidelines for the treatment of gout recommend starting allopurinol at a daily dose of 100 mg in patients with normal renal function, escalating to 800 mg (or more) as needed to control hyperuricemia.⁶ Patients with gout and renal failure usually receive a lower starting dose of allopurinol, 50 mg daily, and maintenance doses are frequently range from 100–300 mg per day.^{6, 7} This reduction in allopurinol dosage is made owing to increased exposure to the allopurinol metabolite, oxypurinol, in patients with renal insufficiency or failure, which increases the risk of AHS in these patients.⁷ A starting dose of 1.5 mg per unit of estimated glomerular filtration rate has been associated with an increased risk of AHS, indicating that initial allopurinol dose is an important factor in AHS.⁸ Typically, AHS develops within weeks or a few months after initiating allopurinol treatment. Together, these observations support a lower starting dose of allopurinol, as endorsed by Hershfield and colleagues.⁴ Hershfield *et al.*⁴ also advised against the use of allopurinol for the treatment of asymptomatic hyperuricemia (that is, in absence of gout), given the risk of AHS and considering that treatment of asymptomatic hyperuricemia with allopurinol has not been unequivocally shown to be beneficial, at present. Other groups have made similar recommendations, although controversy exists in this area. Hershfield *et al.* recommended that given the high specificity for allopurinol-induced SCAR, allopurinol should not be prescribed to patients who have tested positive for HLA-B*58:01.⁴ They recommended that alternative medications should be considered for these patients to avoid the risk of developing SCAR. For patients who have tested negative, allopurinol may be prescribed as usual. They recognized that testing negative for HLA-B*58:01 does not totally eliminate the possibility of developing SCAR, especially in the European population

A diagnostic kit is currently commercially available for testing for the presence of the HLAB*5801 allele. For example, positive predictive values (PPV) and negative predictive values (NPV) of HLA-B*5801 for AHS were ~1.5% and 100%, respectively, in Han-Chinese and Thai population.⁹ As can be seen, HLA-B*5801 provides excellent NPV, but the positive predictive value is much lower. This slight improvement in PPV is due to a lower overall of HLA-B*5801 allele carrier frequency in European populations compared with Asian populations.

Testing negative for HLA-B*5801 does not totally eliminate the possibility of developing AHS, especially in the European population.^{4, 5} On the other hand, testing negative for this allele can eliminate the possibility of developing AHS, for example, in Thai or Han Chinese populations.^{4, 5} Nonetheless, caution is needed as these observations are based on single

studies within each population, and additional studies are required to add more confidence and clarity to genetics of AHS, especially in European populations

Certain aspects of testing for HLA-B*5801 allele meet the criteria for a good screening test: the disease (AHS in this case) has serious consequences; the screening test detects disease before a critical point, causes little morbidity and is available (as well as being potentially affordable, in this case); intervention is available if test is positive (use of other medications for treatment of gout); and the test is not toxic or otherwise pose a high risk.¹⁰ On the other hand, the HLA-B*5801 genotyping test does possess the accuracy needed to detect more true-positive than false-positive cases of AHS and will detect pseudodisease in some populations, and the prevalence of the condition (AHS) is low, limiting the utility of the test.¹⁰ Thus, as a single test, HLA-B*5801 genotyping is not foolproof in all populations, as most patients found to have HLA-B*5801 allele will not develop AHS, given the rarity of this SCAR. Therefore, detection of new genetic factors that further improve the predictive value of HLA-B*5801 allele for AHS are needed, before this biomarker can be used effectively in the clinic. The effectiveness of such a screening test is also likely to differ between populations, owing to differences in the baseline prevalence of the alleles used and the associated risk of AHS. In this respect, HLA-B*5801, which seems to be much less prevalent in white populations compared with Asian populations,⁴ represents a key example.

Prior to the discovery of association of HLA-B*58:01 with AHS, use of diuretics and concomitant antibiotics were reported as risk factors for AHS; more data are needed to examine whether these associations hold true. Despite being challenging to study owing to rarity of AHS, well-designed can enable identification of novel risk factors and confirmation of suspected risk factors for allopurinol-associated SCARs. Such studies might aid the construction of a robust risk prediction measure incorporating HLA-B*5801 status (and additional alleles identified as genetic risk factors) and clinical variables. Given the high mortality associated with AHS, the importance of early diagnosis and treatment of the condition is obvious; however, practical strategies to prevent AHS are likely to prove far more effective and important.

The unfolding of HLA-B*5801 story has really opened a new area of investigation in pharmacogenomics in gout management and has improved our understanding of AHS and SCARs by leaps and bounds. As more studies replicate these innovative findings and identify new genetic and clinical risk factors, we might soon arrive at a point where we are able to predict AHS with greater certainty. Such advances will enable us to save the lives of people at risk of this rare, sometime fatal, adverse effect of a commonly used medication, allopurinol, which is otherwise well tolerated and effective when used at the appropriate doses in patients with gout.

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Biography

Dr. Singh is an Associate professor of medicine and epidemiology at the University of Alabama at Birmingham, a staff rheumatologist at the Birmingham Veterans Affairs Medical center and a research collaborator at the Mayo Clinic College of Medicine, Rochester, MN. He is interested in patient-reported and other outcomes in patients with gout, osteoarthritis in those with joint arthroplasty. Dr. Singh is involved with performing Cochrane systematic reviews and developing treatment guidelines. Dr. Singh is a member of OMERACT, an international organization of scientists that develops validated outcome measures in rheumatology.

Based on Figure 2 from Hershfield et al.

Figure 1.

Treatment recommendations from Hershfield et al. based on HLA-B*58:01 testing