HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol

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摘要

Abstract

Allopurinol, a commonly prescribed medication for gout and hyperuricemia, is a frequent cause of severe cutaneous adverse reactions (SCAR), which include the drug hypersensitivity syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis. The adverse events are unpredictable and carry significant morbidity and mortality. To identify genetic markers for allopurinol-SCAR, we carried out a case-control association study. We enrolled 51 patients with allopurinol-SCAR and 228 control individuals (135 allopurinol-tolerant subjects and 93 healthy subjects from the general population), and genotyped for 823 SNPs in genes related to drug metabolism and immune response. The initial screen revealed strong association between allopurinol-SCAR and SNPs in the MHC region, including BAT3 (encoding HLA-B associated transcript 3), MSH5 (mutS homolog 5), and MICB (MHC class I polypeptide-related sequence B) ($P < 10(-7)$). We then determined the alleles of HLA loci A, B, C, and DRB1. The HLA-B*5801 allele was present in all (100%) 51 patients with allopurinol-SCAR, but only in 20 (15%) of 135 tolerant patients [odds ratio 580.3 (95% confidence interval, 34.4-9780.9); corrected P value = 4.7 x 10(-24)] and in 19 (20%) of 93 of healthy subjects [393.51 (23.23-6665.26); corrected P value = 8.1 x 10(-18)]. HLA alleles A*3303, Cw*0302, and DRB1*0301 were in linkage disequilibrium and formed an extended haplotype with HLA-B*5801. Our results indicated that allopurinol-SCAR is strongly associated with a genetic predisposition in Han Chinese. In particular, HLA-B*5801 allele is an important genetic risk factor for this life-threatening condition.