

Genetic susceptibility to carbamazepine-induced cutaneous adverse reactions

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摘要

Abstract

The anticonvulsant carbamazepine (CBZ) frequently causes cutaneous adverse drug reactions (cADRs), including maculopapular eruption (MPE), hypersensitivity syndrome (HSS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). We reported that SJS/TEN caused by CBZ is strongly associated with the HLA-B*1502 gene in Han Chinese. Here, we extended our genetic study to different types of CBZ-cADRs (91 patients, including 60 patients with SJS/TEN, 13 patients with hypersensitivity syndrome and 18 with maculopapular exanthema versus 144 tolerant controls). We used MALDI-TOF mass spectrometry to screen the genetic association of 278 single nucleotide polymorphisms (SNPs), which cover the major histocompatibility complex (MHC) region, tumor necrosis factor- α , heat shock protein and CBZ-metabolic enzymes, including CYP3A4, 2B6, 2C8, 2C9, 1A2 and epoxide hydrolase 1. In addition, we genotyped 20 microsatellites in the MHC region and performed HLA-typing to construct the recombinant map. We narrowed the susceptibility locus for CBZ-SJS/TEN to within 86 kb flanking the HLA-B gene on the extended B*1502 haplotype, and confirmed the association of B*1502 with SJS/TEN [$P_c=1.6 \times 10^{-6}$, odds ratio (OR)=1357; 95% confidence interval (CI)=193.4-8838.3]. By contrast to CBZ-SJS/TEN, HLA-B*1502 association was not observed in the MPE or HSS groups: MPE was associated with SNPs in the HLA-E region and a nearby allele, HLA-A*3101 ($P_c=2.2 \times 10^{-4}$, OR=17.5; 95% CI=4.6-66.5), and HSS with SNPs in the motilin gene ($P_c=0.0064$, OR=7.11; 95% CI=3.1-16.5) located terminal to the MHC class II genes. No SNPs in genes involved in CBZ metabolism were

associated with CBZ-induced cADRs. Our data suggest that HLA-B*1502 could contribute to the pathogenesis of CBZ-SJS/TEN, and that genetic susceptibility to CBZ-induced cADRs is phenotype-specific.