

OF RACE, ETHNICITY, AND RASH: THE GENETICS OF ANTIEPILEPTIC DRUG-INDUCED SKIN REACTIONS

Association between HLA-B*1502 Allele and Antiepileptic Drug-Induced Cutaneous Reactions in Han Chinese.

Man CB, Kwan P, Baum L, Yu E, Lau KM, Cheng AS, Ng MH. *Epilepsia* 2007;48(5):1015–1018. A previous study conducted in Taiwan found a 100% association between HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome (SJS) in Han Chinese subjects, with an extremely high odds ratio compared with carbamazepine-tolerant subjects (odds ratio = 2,504). We examined this association in 24 Hong Kong Han Chinese subjects who had cutaneous adverse reactions induced by different antiepileptic drugs (AEDs). They were matched with 48 AED-tolerant controls. HLA-B*1502 was associated with severe cutaneous reactions (SCR) induced by AEDs, which included carbamazepine, phenytoin, and lamotrigine ($p = 0.001$, odds ratio = 17.6), but was not associated with maculopapular exanthema (MPE) ($p = 0.32$). Further studies in larger samples of ethnically matched subjects should be conducted to confirm the findings. Identification of genetic polymorphisms predisposing to development of AED-induced SCR offers the possibility of avoiding these high-risk drugs in genetically susceptible individuals.

COMMENTARY

Serious allergic cutaneous reactions, especially Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), are among the most feared complications of antiepileptic drug (AED) therapy. SJS and TEN are characterized by a blistering exanthema with mucosal involvement and skin detachment. TEN is defined by more extensive skin involvement than SJS (>30%) and has a higher mortality rate, 25% or more. The risk of these rare conditions colors many epilepsy treatment decisions, influencing the choice of an AED and the speed at which it is initiated. For this reason, the emerging evidence that genetic factors strongly predict occurrence of SJS and TEN will most certainly lead to changes in clinical practice.

SJS/TEN is reportedly two to three times more prevalent in Han Chinese than Caucasians (1), with carbamazepine use associated with 25 to 33% of cases for Asians (2) compared with 5–6% for Europeans (3). These differences have now been explained by demonstration of a close association between the two conditions and the human leukocyte antigen, *HLA-B*1502* (2,4). The most comprehensive study found that 59 of 60 Han Chinese patients in Taiwan with carbamazepine-induced SJS or TEN had the *HLA-B*1502* allele, as compared with 6 of 144 control subjects and 1 of 31 patients with carbamazepine-induced maculopapular eruption (MPE) or hypersensitivity syndrome (HSS, defined as a rash accompanied by multiorgan involvement, such as hepatitis and nephritis, and systemic symptoms, such as fever and arthralgias) (4).

The SJS/TEN susceptibility locus maps tightly to the region of the *HLA-B* gene (4). The strong linkage suggests that the product of this gene may have a direct functional role in drug hypersensitivity. It has been proposed that the *HLA-B*1502*

allele codes for a molecule that is displayed on the surface of antigen-presenting cells (5). Carbamazepine or a metabolite, combined with an unknown peptide, binds to this molecule, which then activates naive CD8+ T lymphocytes that, in turn, proliferate, leading to SJS/TEN. The lack of association between carbamazepine-induced MPE/HSS and *HLA-B*1502* suggests that it may be mediated by somewhat different immune mechanisms than SJS/TEN.

*HLA-B*1502* has a strikingly variable occurrence among different ethnic groups, which has been only partially defined. It occurs in 10–15% of individuals from southern China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan (6) and has a prevalence rate of 2–4%, or higher, in other southern Asian groups, including Indians. It is uncommon in Japan and Korea (<1%) (6) and in European Caucasians (0–0.1%) (5). Remarkably, one study of 12 French and German patients with carbamazepine-induced SJS/TEN found that all 4 *HLA-B*1502*-positive individuals had Asian ancestry.

Other *HLA-B* alleles have been shown to predispose patients to different hypersensitivity reactions to drugs other than carbamazepine (5). For instance, *HLA-B*5801* is strongly predictive of SJS/TEN/HSS from allopurinol (5); this allele is found in most populations but is more prevalent in Asian Indians (3–15%) and Chinese (8.8–10.9%). Similarly, *HLA-B*5701* predicts MPE/HSS to abacavir in Caucasians but not patients of African or Hispanic descent.

The work by Man et al. offers strong confirmation of the earlier reports from Taiwan (1,4), with *HLA-B*1502* being found in 6 of 6 SJS/TEN cases, 2 of 18 MPE/HSS cases, and 7 of 48 control subjects. However, new concerns are raised as the *HLA-B*1502*-positive SJS/TEN group included two patients not exposed to carbamazepine, one having been started on phenytoin and the other on lamotrigine. Unfortunately, the true risk of phenytoin and lamotrigine exposure in *HLA-B*1502*-positive patients cannot be deduced from single cases.

A recent FDA alert recommends that patients with ancestry from at-risk populations be screened for the *HLA-B* 1502* allele prior to starting carbamazepine and that positive patients not be exposed to it (6). The feasibility and benefits of *HLA-B* 5701* screening for abacavir have already been well documented (7). Although a cost–benefit analysis is not yet available for genetic screening for carbamazepine hypersensitivity, the arguments for performing it are compelling in high-risk populations, considering the severe consequences of SJS/TEN and the fact that high-resolution HLA-B screening for B*1502 should cost approximately \$200 in the United States and would delay drug initiation by only 1–2 days.

Although genetic screening is a promising method to predict and reduce occurrence of carbamazepine-induced severe cutaneous reactions, major uncertainties remain that make it difficult for the clinician to apply this new tool with confidence. What is the prevalence of the *HLA-B* 1502* allele in patients with African, Middle Eastern, Hispanic, and Native American ancestry? What is the risk of SJS/TEN when *HLA-B* 1502*-positive patients are started on other AEDs such as lamotrigine, or phenytoin? Are there additional, undiscovered, strong predictors of AED hypersensitivity for other ethnic groups? These questions can be addressed by further studies using current methods. The answers will lead to safer treatment of epilepsy.

by John W. Miller, MD, PhD

References

1. Chung WH, Hung SI, Hong HS, Hsieh MS, Yang LC, Ho HC, Wu JY, Chen YT. A marker for Stevens-Johnson syndrome. *Nature* 2004;428(1):486.
2. Kamaliah MD, Zainal D, Mokhtar N, Nazmi N. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in northeastern Malaysia. *Int J Dermatol* 1998;37(7):520–523.
3. Roujeau JC, Kelly JP, Naldi L, Rzany B, Stern RS, Anderson T, Auquier A, Bastuji-Garin S, Correia O, Locati F. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995;333(24):1600–1607.
4. Hung SL, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, Hu SL, Wu MT, Chen GS, Wong TW, Hsiao, Chen WH, Shih HY, Fang WH, Wei CY, Lou YH, Huang YL, Lin JJ, Chen YT. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenet Genomics* 2006;16(4):297–306.
5. Chung WH, Hung SL, Chen YT. Human leucocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2007;7:317–323.
6. Information for healthcare professionals. Carbamazepine (marketed as Carbatrol, Equetro, Tegretol and generics). FDA Alert 12/12/07, updated 1/31/08; Available at: <http://www.fda.gov/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm>. [Accessed June 30, 2008].
7. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006;43(1):99–102.