

HLA-B*1502 Screening and Toxic Effects of Carbamazepine

TO THE EDITOR: Chen et al. (March 24 issue)¹ report the absence of the Stevens–Johnson syndrome and its related disease, toxic epidermal necrolysis (SJS–TEN), in subjects who were screened for the HLA-B*1502 allele and were advised not to take carbamazepine if they carried the allele. Case–control studies involving subjects of Han Chinese and Thai origin have also shown an association between SJS–TEN and the receipt of phenytoin, lamotrigine, and oxcarbazepine among HLA-B*1502 carriers.^{2–4} The Food and Drug Administration has stated that “healthcare providers should consider avoiding phenytoin as alternatives for CBZ [carbamazepine] in patients who test positive for HLA-B*1502.”⁵ Chen et al. state that lamotrigine and oxcarbazepine were among the alternative medications offered to HLA-B*1502 carriers and did not indicate whether the investigators or treating physicians warned patients not to take phenytoin. The increasing use of HLA-B*1502 screening to prevent carbamazepine-induced SJS–TEN will lead to the replacement of this drug with other anticonvulsants among HLA-B*1502 carriers. Given the availability of other elective therapeutic choices, it may be prudent to advise HLA-B*1502 carriers to avoid not only carbamazepine but also other structurally related anticonvulsants, such as phenytoin, oxcarbazepine, and possibly lamotrigine.

Elizabeth J. Phillips, M.D.

Simon A. Mallal, M.B., B.S.

Institute for Immunology and Infectious Diseases
Murdoch, WA, Australia
e.phillips@iivid.com.au

No potential conflict of interest relevant to this letter was reported.

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2. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007;48:1015-8. [Erratum, *Epilepsia* 2008;49:941.]
3. Hung SI, Chung WH, Liu ZS, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics* 2010;11:349-56.
4. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;49:2087-91. [Erratum, *Epilepsia* 2009;50:971.]
5. FDA alert: phenytoin and fosphenytoin information. Silver Spring, MD: Food and Drug Administration, November 24, 2008. (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm110259.htm>.)

TO THE EDITOR: Chen et al. report that SJS–TEN did not develop in subjects testing negative for HLA-B*1502 who received carbamazepine. After genotyping HLA-B in 11 patients who had carbamazepine-induced SJS–TEN and who were of southern Han Chinese origin, we observed that 3 of these patients were negative for HLA-B*1502. Rather, they carried HLA-B*1511/1511, 5401/5401, and 4001/4601. Some early studies¹ suggested that Han Chinese persons with carbamazepine-induced SJS–TEN who lived in Taiwan, Hong Kong, or some Southeast Asian countries were almost all HLA-B*1502 carriers. More recent studies have reported more instances of SJS–TEN among persons who were negative for HLA-B*1502.²

Since it has been reported that European and Japanese patients with carbamazepine-induced SJS–TEN were negative for HLA-B*1502,³ we suggest that the risk of this disorder is not nil in such patients and that physicians should be vigilant about the possibility of this disorder in patients receiving carbamazepine, regardless of their HLA-B genotype.

Wei-Ping Liao, M.D., Ph.D.

Second Affiliated Hospital of Guangzhou Medical University
Guangzhou, China
wpliao@tom.com

Yi-Wu Shi, Ph.D.

Fu-Li Min, M.D.

Key Laboratory of Neurogenetics and Channelopathies
of Guangdong Province
Guangzhou, China

No potential conflict of interest relevant to this letter was reported.

1. Locharernkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia* 2008;49:2087-91. [Erratum, *Epilepsia* 2009;50:971.]
2. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia* 2010;51:926-30.
3. Chung WH, Hung SI, Chen YT. Genetic predisposition of life-threatening antiepileptic-induced skin reactions. *Expert Opin Drug Saf* 2010;9:15-21.

THE AUTHORS REPLY: We agree with Phillips and Mallal that it is important to advise HLA-B*1502 carriers to avoid not only carbamazepine but also other structurally related anticonvulsants, such as phenytoin, oxcarbazepine, and lamotrigine. In a recent study,¹ we found that when these drugs were associated with SJS–TEN, the patients shared a common risk allele (i.e., HLA-B*1502), so the drugs may act on a similar pathogenic mechanism. We do not exclude the possibility of the pathogenic contribution of other alleles to carbamazepine-induced SJS–TEN, such as those described by Liao et al. However, to test whether associations with such alleles are significant requires a case–control study comparing the prevalence of these alleles in persons with carbamazepine-induced SJS–TEN and their prevalence in persons tolerant of carbamazepine.

Pei Chen, Ph.D.

Yuan-Tsong Chen, M.D., Ph.D.

Chen-Yang Shen, Ph.D.

Academia Sinica
Taipei, Taiwan
bmcys@ibms.sinica.edu.tw

Since publication of their article, the authors report no further potential conflict of interest.

1. Hung SI, Chung WH, Liu ZS, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics* 2010;11:349-56.