ORIGINAL ARTICLE

# Carbamazepine-Induced Toxic Effects and HLA-B*1502 Screening in Taiwan

Pei Chen, Ph.D., Juei-Jueng Lin, M.D., Chin-Song Lu, M.D., Cheung-Ter Ong, M.D., Peiyuan F. Hsieh, M.D., Chih-Chao Yang, M.D., Chih-Ta Tai, M.D., Shey-Lin Wu, M.D., Cheng-Hsien Lu, M.D., Yung-Chu Hsu, M.D., Hsiang-Yu Yu, M.D., Long-Sun Ro, M.D., Chung-Ta Lu, M.D., Chun-Che Chu, M.D., Jing-Jane Tsai, M.D., Yu-Hsiang Su, M.D., Sheng-Hsing Lan, M.D., Sheng-Feng Sung, M.D., Shu-Yi Lin, M.S., Hui-Ping Chuang, B.S., Li-Chen Huang, B.S., Ying-Ju Chen, M.S., Pei-Joung Tsai, M.S., Hung-Ting Liao, M.S., Yu-Hsuan Lin, M.S., Chien-Hsiun Chen, Ph.D., Wen-Hung Chung, M.D., Ph.D., Shuen-Iu Hung, Ph.D., Jer-Yuarn Wu, Ph.D., Chi-Feng Chang, Ph.D., Luke Chen, Ph.D., Yuan-Tsong Chen, M.D., Ph.D., and Chen-Yang Shen, Ph.D., for the Taiwan SJS Consortium*

## ABSTRACT

### BACKGROUND

Carbamazepine, an anticonvulsant and a mood-stabilizing drug, is the main cause of the Stevens–Johnson syndrome (SJS) and its related disease, toxic epidermal necrolysis (TEN), in Southeast Asian countries. Carbamazepine-induced SJS–TEN is strongly associated with the HLA B*1502 allele. We sought to prevent carbamazepine-induced SJS–TEN by using HLA-B*1502 screening to prospectively identify subjects at genetic risk for the condition.

### METHODS

From 23 hospitals in Taiwan, we recruited 4877 candidate subjects who had not taken carbamazepine. We genotyped DNA purified from the subjects' peripheral blood to determine whether they carried the HLA-B*1502 allele. Those testing positive for HLA-B*1502 (7.7% of the total) were advised not to take carbamazepine and were given an alternative medication or advised to continue taking their prestudy medication; those testing negative (92.3%) were advised to take carbamazepine. We interviewed the subjects by telephone once a week for 2 months to monitor them for symptoms. We used the estimated historical incidence of SJS–TEN as a control.

### RESULTS

Mild, transient rash developed in 4.3% of subjects; more widespread rash developed in 0.1% of subjects, who were hospitalized. SJS–TEN did not develop in any of the HLA-B*1502–negative subjects receiving carbamazepine. In contrast, the estimated historical incidence of carbamazepine-induced SJS–TEN (0.23%) would translate into approximately 10 cases among study subjects ($P<0.001$).

### CONCLUSIONS

The identification of subjects carrying the HLA-B*1502 allele and the avoidance of carbamazepine therapy in these subjects was strongly associated with a decrease in the incidence of carbamazepine-induced SJS–TEN. (Funded by the National Science Council of Taiwan and the Taiwan Drug Relief Foundation.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Shen or Dr. Y.-T. Chen at the Institute of Biomedical Sciences, Academia Sinica, 128 Academia Rd., Section 2, Nankang, Taipei 115, Taiwan, or at bmcys@ibms.sinica.edu.tw or chen0010@ibms.sinica.edu.tw.

*Other members of the Taiwan Stevens–Johnson Syndrome (SJS) Consortium are listed in the Supplementary Appendix, available at NEJM.org.

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The Stevens–Johnson syndrome (SJS) and its related disease, toxic epidermal necrolysis (TEN), are two of the most serious adverse reactions caused by drugs. SJS is characterized by high fever, malaise, and a rapidly developing, blistering exanthema of macular papules and target-like lesions, accompanied by mucosal involvement. This condition is associated with a rate of death of approximately 5%. TEN has a similar presentation, with even more extensive skin detachment and a death rate of 25 to 35%.[1] Carbamazepine, an anticonvulsant and specific analgesic agent for trigeminal neuralgia, is the most common cause of SJS–TEN in Southeast Asian countries.[2] We previously reported that carbamazepine-induced SJS–TEN is strongly associated with the HLA-B*1502 allele in Han Chinese populations.[3] This association was subsequently confirmed in persons from Hong Kong, Malaysia, Thailand, and India and in descendants of immigrants from Southeast Asia, regions in which the HLA-B*1502 allele is prevalent.[4-9] Another HLA allele, HLA-A*3101, has been associated with carbamazepine-induced hypersensitivity reactions. We have observed its association with the relatively mild maculopapular exanthema.[10] More recently, a genomewide association study has shown an association between the HLA-A*3101 allele and SJS–TEN in Japanese persons,[11] and a report in this issue of the *Journal* shows the association between this allele and a range of hypersensitivity reactions, including SJS–TEN, in persons of European descent.[12]

Among persons of Han Chinese descent, carbamazepine-induced SJS–TEN almost never occurs in noncarriers of the HLA-B*1502 allele, evidence that this allele is directly involved in the pathogenesis of the condition. Carbamazepine directly binds to HLA-B molecules on antigen-presenting T cells and contributes to cell death mediated by cytotoxic T cells in persons with SJS–TEN.[13] HLA-B*1502 can directly present carbamazepine to cytotoxic T cells without antigen processing. More important, carbamazepine-specific T-cell–mediated cytotoxicity is restricted to HLA-B*1502.[14]

The risk of carbamazepine-induced SJS–TEN is significantly higher among persons of Chinese origin who carry the HLA-B*1502 allele than among those who do not carry the allele (odds ratio, 1357; 95% confidence interval, 193 to 8838; $P=1.6\times10^{-41}$).[10] If HLA-B*1502 were used as a marker to predict carbamazepine-induced SJS–TEN, the test would have a high sensitivity (98.3%) and specificity (95.8%). On the basis of an incidence of carbamazepine-induced SJS–TEN of 0.25%, this allele would have a negative predictive value of 99.9% and a positive predictive value of 5.6%. The use of HLA-B*1502 genotyping to prevent carbamazepine-induced SJS–TEN in routine clinical practice thus seems warranted. We conducted a study to determine whether prospective screening by means of HLA-B*1502 genotyping before deciding on carbamazepine treatment reduces the incidence of carbamazepine-induced SJS–TEN.

## Methods

### Study Design

We recruited subjects from 23 participating hospitals throughout Taiwan (see the Supplementary Appendix, available with the full text of this article at NEJM.org). To ensure that all investigational sites complied with all applicable regulations and protocol requirements, an independent contract research organization (CRO Service Division, Formosa Biomedical Technology) monitored the study.

We had 9 points of interaction with HLA-B*1502–negative subjects and 10 points of interaction with HLA-B*1502 carriers: the first screening visit, a second clinic visit for HLA-B*1502 carriers only, and weekly telephone interviews during the 2-month follow-up period. Subjects between the ages of 6 months and 99 years who had not previously received carbamazepine and who would normally have received it at the time of screening were invited to participate in the study.

We excluded subjects who had a history of carbamazepine allergy, those who had undergone bone marrow transplantation, and those who were not of Han Chinese descent. Status with respect to Han Chinese descent was determined with the use of a multiple-choice questionnaire that asked the subjects to identify the ethnic group of their parents and grandparents.

We prescribed and provided carbamazepine to all subjects at the time of the screening visit, but we requested that they defer taking the drug until we had obtained and relayed to them their

genetic test results. Blood samples were collected and transferred to a central laboratory (Institute of Biomedical Sciences, Academia Sinica) for HLA-B*1502 genotyping, and the results were reported to the participating physicians within 2 to 3 days.

We asked HLA-B*1502–positive subjects to return to the clinic within 3 days, at which point we explained to them the risk of carbamazepine-induced SJS–TEN and recommended alternative drugs or therapy. HLA-B*1502–negative subjects (who also were counseled about the risk of SJS–TEN) were started on carbamazepine. Because the onset of SJS–TEN occurs within 2 months after the initiation of carbamazepine therapy,[10] we interviewed all subjects by telephone during the 2-month period after the screening visit (for HLA-B*1502–negative subjects) or after the second clinic visit (for HLA-B*1502 carriers) to monitor them for symptoms of adverse drug reactions, including SJS–TEN. We asked subjects to return to the hospital immediately to be evaluated by a dermatologist in the event that early symptoms of SJS–TEN developed. We monitored all subjects (aside from those who were lost to follow-up) throughout the study.

We performed the study in accordance with Good Clinical Practice Standards and the provisions of the Declaration of Helsinki. The study protocol was approved by the research ethics committee at Academia Sinica and by the institutional review board at each participating hospital. Written informed consent was obtained from all subjects or from parents or guardians for subjects who were under 21 years of age. The study was conducted in accordance with the protocol.

### GENOTYPING OF HLA-B*1502

We obtained 2 ml of whole blood from each subject in a Monovettes tube, stored the sample at 4 to 12°C, and sent it to Academia Sinica on the same day that we obtained it. Genomic DNA was isolated with the use of the QIAamp DNA purification system (Qiagen). The presence or absence of the HLA-B*1502 allele was determined with the use of the PG1502 DNA detection kit (Pharmigene), according to the manufacturer's instructions. The kits are based on real-time polymerase-chain-reaction assay, with sequence-specific primers for HLAB*1502. To validate the results of the PG1502 DNA detection kit, the first 2000 samples were also tested in parallel by HLA sequence-specific oligonucleotide reverse line blot (Dynal Biotech). In each of these 2000 samples, the results that were obtained with the use of the PG1502 DNA kit were consistent with those obtained with the use of the line-blot assay.

### ANNUAL INCIDENCE

The estimated number of SJS–TEN cases was based on diagnostic code 695.1 for erythema multiforme in the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). We obtained the number of subjects with this code from the National Health Insurance Research Database (NHIRD), provided by the Bureau of National Health Insurance of the Department of Health. We calculated the annual incidence of carbamazepine-induced SJS–TEN in Taiwan as the annual number of cases of SJS–TEN caused by carbamazepine divided by the annual number of new carbamazepine recipients. A previous 5-year retrospective study (1997–2002), in which a dermatologist reviewed the medical records of 700 subjects with ICD-9-CM code 695.1 in the Chang-Gung Memorial Hospital system, suggested that among 230 subjects with SJS–TEN, 60 had taken carbamazepine; SJS–TEN had developed in the remaining 170 subjects after they had received other drugs.[2] We therefore assumed that 32.9% of subjects with ICD-9-CM diagnostic code 695.1 had SJS–TEN and that the disease would be caused by carbamazepine in 26.1% of these subjects. Thus, we calculated the annual number of cases of carbamazepine-induced SJS–TEN as the number of subjects with ICD-9-CM diagnostic code 695.1 multiplied by 32.9% (the estimated proportion of subjects in Taiwan with ICD-9-CM diagnostic code 695.1 who would have SJS or TEN) multiplied by 26.1% (the estimated proportion of cases of carbamazepine-induced SJS–TEN among all those with SJS–TEN in Taiwan).

Since it usually takes at least 14 days for SJS–TEN to develop after the initiation of carbamazepine treatment, we obtained data for years 2001, 2002, 2003, and 2004 from the NHIRD regarding the number of persons who received new prescriptions for at least 14 days of carbamazepine each year.

### STATISTICAL ANALYSIS

On the basis of the prevalence of the HLA-B*1502 allele (8%) in the Taiwanese population,[3] we de-

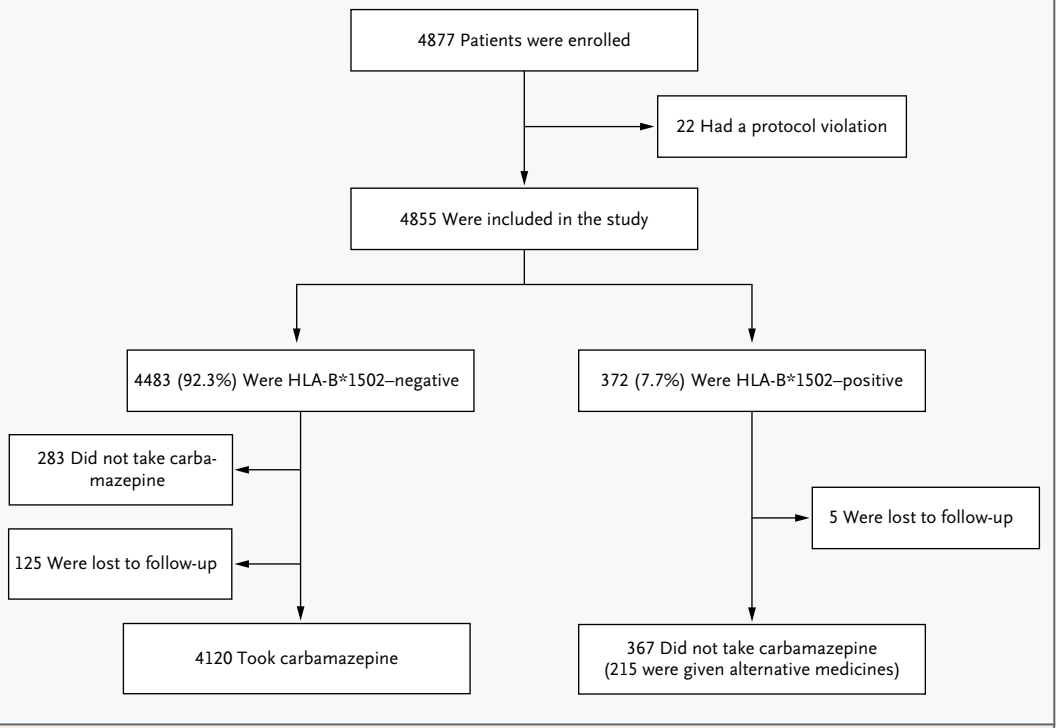


**Figure 1. Enrollment and Outcomes.**

Carbamazepine was prescribed and provided for all subjects at the time of the screening visit, but they were asked to defer taking the drug until the results of genetic testing were available to them. All subjects, regardless of HLA-B status, were followed for 2 months, with weekly telephone interviews.

termined that 4419 subjects would provide a power of 99% to detect a reduction in the incidence of carbamazepine-induced SJS–TEN from 0.25% (i.e., 25 cases per 10,000 new recipients[2]) to 0.03%. We used Fisher's exact to compare the rate of carbamazepine-induced SJS–TEN in the prospective screening population with the historical incidence. All reported P values are two-tailed, and a P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### SUBJECTS

From July 2007 through April 2010, we enrolled 4877 subjects, of whom 4855 underwent genotyping and were included in the 2-month follow-up (Fig. 1). There were about equal numbers of men and women, with a mean age of 56.5 years (range, 0.6 to 98.2) for all subjects (Table 1). Indications for carbamazepine treatment included epilepsy (14.2% of subjects), neuralgia (54.1%), diabetes-related neuropathic pain (11.7%), tinnitus (3.6%), and bipolar disorder or other psychiatric disorders (2.8%) (Table 1).

### SCREENING FOR HLA-B*1502

Of the 4855 subjects who were included in the study, 372 (7.7%) were found to carry the HLA-B*1502 allele and were advised not to take carbamazepine. These subjects were prescribed alternative medications or advised to continue taking their prestudy medication; all were monitored for adverse events. Of these subjects, 5 were lost to follow-up, 215 took an alternative medication, and 152 continued taking their prestudy medication (Fig. 1). Alternative medications included gabapentin, valproic acid, oxcarbazepine, imipramine, clonazepam, and lamotrigine. The remaining 4483 subjects (92.3%) were HLA-B*1502–negative. Of these subjects, 238 did not take carbamazepine and 125 were lost to follow-up, leaving 4120 HLA-B*1502–negative subjects who took the drug and were monitored (Fig. 1).

**Table 1. Characteristics of the Subjects.**

| Characteristic | HLA-B*1502–Positive (N=372) | HLA-B*1502–Negative (N=4483) | Total (N=4855) |
|---|---|---|---|
| Sex — no. (%) | | | |
| Male | 193 (51.9) | 2132 (47.6) | 2325 (47.9) |
| Female | 179 (48.1) | 2351 (52.4) | 2530 (52.1) |
| Age — yr | | | |
| Mean | 55.7 | 56.5 | 56.5 |
| Range | 4.3–91.4 | 0.6–98.2 | 0.6–98.2 |
| Indication for carbamazepine — no. (%) | | | |
| Epilepsy | 57 (15.3) | 632 (14.1) | 689 (14.2) |
| Neuralgia | 195 (52.4) | 2430 (54.2) | 2625 (54.1) |
| Diabetes-related neuropathic pain | 53 (14.2) | 515 (11.5) | 568 (11.7) |
| Tinnitus | 8 (2.2) | 168 (3.7) | 176 (3.6) |
| Bipolar or other psychiatric disorder | 12 (3.2) | 122 (2.7) | 134 (2.8) |
| Other conditions* | 47 (12.6) | 647 (14.4) | 694 (14.3) |

* These conditions include herpes zoster, unspecified cerebral-artery occlusion, meralgia paresthetica, and multiple sclerosis.

### ADVERSE EVENTS

Among all 4855 subjects, mild and transient rash and itching developed in 211 (4.3%), including 21 subjects who had a combination of rash, itching, and localized blisters and 26 subjects who had limited oral ulcers (Table 2). Of the 211 subjects with rash or itching, 5 were HLA-B*1502–positive and presented with symptoms after taking alternative drugs (gabapentin, lamotrigine, naproxen, imipramine, or prednisolone) (Table 2). In addition, 7 subjects had more severe cutaneous symptoms — maculopapular eruption (in 3 subjects), hypersensitivity syndrome (in 2 subjects), and urticaria (in 2 subjects) — for which they were hospitalized. One of the two subjects with urticaria was HLA-B*1502–positive and had taken oxcarbazepine before study enrollment. None of the subjects received a diagnosis of SJS–TEN.

Other adverse events included fever, sore throat, fatigue, dizziness, insomnia, and gastrointestinal symptoms. These events occurred in both HLA-B*1502–positive and HLA-B*1502–negative subjects.

### HISTORICAL INCIDENCE

The NHIRD data showed that carbamazepine was prescribed for at least 14 days for 50,917 persons in 2002, 48,522 in 2003, and 49,670 in 2004 who had not previously received carbamazepine, at least dating back to the beginning of the previous calendar year (Table 3). We therefore calculated that the incidence of SJS–TEN in 2002, 2003, and 2004 in Taiwan was 0.24%, 0.22%, and 0.23%, respectively. We used the mean (0.23%) as the historical incidence for further analysis.

### INCIDENCE OF SJS–TEN AFTER GENETIC SCREENING

On the basis of the estimated historical incidence of 0.23%, 10 cases of SJS or TEN would be expected among the 4120 subjects who took carbamazepine in our study. However, there were no cases of either SJS or TEN in any of the subjects, a result that differed significantly from the historical incidence ($P<0.001$ by Fisher's exact test) (Table 3).

## DISCUSSION

Our findings suggest that screening patients for the HLA-B*1502 allele before the initiation of carbamazepine treatment and withholding carbamazepine from HLA-B*1502–positive patients can reduce the incidence of carbamazepine-induced SJS–TEN among Han Chinese. In estimating the historical incidence of this condition, we defined new carbamazepine recipients as those who had not received carbamazepine during the previous year and who were prescribed carbamazepine for at least 14 days in the year of interest, because carbamazepine-induced SJS–TEN is a delayed hypersensitivity reaction that usually takes at least 14 days to develop. However, even if

**Table 2. Adverse Events during the 2-Month Follow-up.**

| Adverse Event | HLA-B*1502–Positive with Alternative Medication (N=215) | HLA-B*1502–Negative with Carbamazepine (N=4120) | Total |
|---|---|---|---|
| | | *number of events* | |
| Mild cutaneous events | | | |
| Rash and itching | 5* | 206 | 211 |
| Rash, itching, and blisters | 1† | 20 | 21 |
| Rash, itching, and oral ulcers | 0 | 14 | 14 |
| Rash, itching, blisters, and oral ulcers | 0 | 7 | 7 |
| Itching, blisters, and oral ulcers | 0 | 2 | 2 |
| Blisters and oral ulcers | 0 | 3 | 3 |
| Severe cutaneous events | | | |
| Maculopapular eruption | 0 | 3 | 3 |
| Hypersensitivity syndrome | 0 | 2 | 2 |
| Urticaria | 1‡ | 1 | 2 |
| Stevens–Johnson syndrome or toxic epidermal necrolysis | 0 | 0 | 0 |
| Other adverse events§ | | | |
| Fever | 1 | 92 | 93 |
| Sore throat | 4 | 126 | 130 |
| Fatigue | 16 | 818 | 834 |
| Dizziness | 10 | 497 | 507 |
| Insomnia | 5 | 197 | 202 |
| Gastrointestinal symptoms | 4 | 185 | 189 |

* Among these 5 subjects, the alternative drugs were gabapentin, lamotrigine, naproxen, imipramine, and prednisolone.
† This subject had rash, itching, and blisters after taking gabapentin as an alternative treatment. These symptoms were mild and disappeared in 7 days.
‡ This subject had taken oxcarbazepine before study enrollment.
§ Subjects may have had more than one adverse event. Adverse events with a low frequency are not listed.

we had included all new carbamazepine recipients, regardless of the duration of treatment, as historical controls, the difference in the incidence of SJS–TEN would still be significant (P=0.01, P=0.02, and P=0.02 for 2002, 2003, and 2004, respectively).

Because we estimated the historical incidence of carbamazepine-induced SJS–TEN on the basis of data obtained from the NHIRD, the reliability of these data is critical for the validity of our estimation. The NHIRD was established in Taiwan when the government launched the National Health Insurance system in 1995. This mandatory single-payer health insurance system, which is administered by the Taiwanese government, provides health care for almost all people in Taiwan, with enrollment of 99.5% of the population in 2008. Of the health care facilities in Taiwan, 92.5% have been contracted by the National Health Insurance system. The NHIRD data were therefore likely to be comprehensive. To estimate both the percentage of subjects with SJS–TEN among those with ICD-9-CM diagnostic code 695.1 (indicating erythema multiforme) and the percentage of cases of carbamazepine-induced SJS–TEN in Taiwan, we based our review on the medical records of 700 cases with diagnostic code 695.1 during a 5-year period at the Chang-Gung Memorial Hospital, the largest hospital system in Taiwan, with several regional centers. This hospital provides health care for about 12% of the Taiwanese population, and its patients are thought to be representative of the general population.

It is possible that some of the drug-related adverse reactions we observed were early SJS lesions or that early withdrawal of carbamazepine may have prevented a more severe SJS–TEN or

**Table 3. Historical Incidence of Carbamazepine-Induced SJS–TEN in 2002, 2003, and 2004, as Compared with the Incidence among Study Subjects.***

| Variable | 2002 | 2003 | 2004 |
|---|---|---|---|
| New recipients of carbamazepine (no.) | 50,917 | 48,522 | 49,670 |
| Subjects with ICD-9-CM diagnostic code 695.1 (no.) | 1441 | 1261 | 1354 |
| Carbamazepine-induced SJS–TEN (no.) | 123 | 108 | 116 |
| Incidence of carbamazepine-induced SJS–TEN (%) | 0.24 | 0.22 | 0.23 |
| P value for comparison between historical incidence and incidence among study subjects† | <0.001 | <0.001 | <0.001 |

* ICD-9-CM denotes *International Classification of Diseases, 9th Revision, Clinical Modification*, and SJS–TEN Stevens–Johnson syndrome and toxic epidermal necrolysis.
† All P values were calculated with the use of Fisher's exact test.

TEN-like reaction. However, we think that this is unlikely, since once patients are sensitized by carbamazepine and have early blisters or ulcers, SJS–TEN progresses, even after the withdrawal of the drug.[15-17] SJS–TEN did not develop in any of the subjects who completed the 2-month follow-up.

Adverse cutaneous reactions, including blisters, oral lesions, and rash, that occurred in the subjects were mild, localized, and transient. In some subjects, blisters developed only after the rash subsided (i.e, blisters were sporadic and tended not to occur at the same time as rash). Furthermore, many HLA-B*1502–negative subjects resumed taking carbamazepine without a recurrence of skin lesions. More important, SJS–TEN did not develop in these subjects, a finding that is consistent with the concept that the incidence of carbamazepine-induced SJS–TEN in HLA-B*1502–negative persons is very low.

Our results suggest the value of HLA-B*1502 screening to prevent carbamazepine-induced SJS–TEN. However, as for any new pharmacogenomic test, it is important to document the use and safety of the alternative medications.[18] Of the 367 HLA-B*1502 carriers, 215 (58.6%) were given an alternative medication, such as gabapentin, valproic acid, oxcarbazepine, imipramine, clonazepam, or lamotrigine; the remainder continued to take their prestudy medication. Among the 215 HLA-B*1502 carriers who took alternative drugs, the only symptom seen during the 2-month follow-up was mild, transient rash in 5 subjects (2.3%).

A strong association between HLA-B*1502 and carbamazepine-induced SJS–TEN has been found in Asian populations other than the Han Chinese,[4-9] including Malay, Thai, and South Asian Indians. In Malaysia, Thailand, and India, studies have shown that carbamazepine was the major cause of drug-induced SJS–TEN. Since the contribution of HLA-B*1502 to carbamazepine-induced SJS–TEN has been proved to be causal,[10,13,14,17] we speculate that in these countries, in which HLA-B*1502 is relatively prevalent, HLA-B*1502 screening could provide a benefit.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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## APPENDIX

The authors' affiliations are as follows: the Institute of Biomedical Sciences, Academia Sinica, Taipei (P.C., S.-Y.L., H.-P.C., L.-C.H., Y.-J.C., P.-J.T., H.-T.L., Y.-H.L., C.-H.C., S.-I.H., J.-Y.W., Y.-T.C., C.-Y.S.); Chu Shang Show Chwan Hospital, Nantou (J.-J.L.); the Departments of Neurology (C.-S.L, L.-S.R., C.-C.C.) and Dermatology (W.-H.C.), Chang-Gung Memorial Hospital at Linkou and College of Medicine, Chang-Gung University, Kweishan; Chia-Yi Christian Hospital, Chia-Yi (C.-T.O., Y.-C.H., Y.-H.S., S.-F.S.); Taichung Veterans General Hospital, Taichung, and National Chi Nan University, Nantou (P.-F.H.); National Taiwan University Hospital, Taipei (C.-C.Y.); Kaohsiung Medical University Chung-Ho Memorial Hospital and Kaohsiung Medical University, Kaohsiung (C.-T.T., S.-H.L.); Changhua Christian Hospital, Changhua (S.-L.W.); Chang-Gung Memorial Hospital at Kaohsiung, Kaohsiung (C-.H.L.); Neurology Department, Taipei Veterans General Hospital and National Yang-Ming University, Taipei (H.-Y.Y.); College of Public Health (C.-Y.S.) and China Medical University Hospital (C.-T.L.), China Medical University, Taichung; National Cheng Kung University Hospital, Tainan (J.-J.T.); Pharmigene (C.-F.C., L.C.); and the Department of Pediatrics, Duke University Medical Center, Durham, NC (Y.-T.C.).

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