Diagnostic Utility of Human Leukocyte Antigen B*15:02 Screening in Severe Carbamazepine Hypersensitivity Syndrome

Youssef Moutaouakkil, Badr Adouani, Yahia Cherrah, Jamal Lamsaouri[1], Yassir Bousliman

Laboratory of Pharmacology-Toxicology and [1]Laboratory of Medicinal Chemistry, Faculty of Medicine and Pharmacy, Rabat Institute
University Mohamed V, Rabat, Morocco

Abstract

Background: Despite many studies suggesting an association between human leukocyte antigen (HLA)-B*15:02 and carbamazepine (CBZ)-induced severe cutaneous adverse drug reactions essentially toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS), the evidence of association in different populations and the degree of association remain uncertain. **Materials and Methods:** The primary analysis was based on population control studies. Data were pooled by means of a random-effects model, and sensitivity, specificity, positive and negative likelihood ratios (LR+ and LR−), diagnostic odds ratios (DOR), and areas under the summary receiver operating characteristic curve (AUC) were calculated. **Results:** In 23 population control studies, HLA-B*15:02 was measured in 373 patients with CBZ-induced TEN/SJS and 3452 patients without CBZ-induced TEN/SJS. The pooled sensitivity, specificity, LR+, LR−, DOR, and AUC were 0.67 (95% confidence interval [CI] = 0.63–0.72), 0.98 (95% CI = 0.98–0.99), 19.73 (95% CI = 10.54–36.92), 0.34 (95% CI = 0.23–0.49), 71.38 (95% CI = 34.89–146.05), and 0.96 (95% CI = 0.92–0.98), respectively. Subgroup analyses for Han Chinese, Thai, and Malaysian populations yielded similar findings. Specifically, racial/ethnic subgroup analyses revealed similar findings with respect to DOR for Han Chinese (99.28; 95% CI = 22.20–443.88), Thai (61.01; 95% CI = 23.05–161.44), and Malaysian (30; 95% CI = 7.08–126.68) populations, which are similar to the pooled DOR for the relationship between the HLA-B*15:02 allele and CBZ-induced TEN/SJS across all populations (71.38; 95% CI = 34.89–146.05). **Conclusions:** The present study reveals that CBZ is the leading cause of TEN/SJS in many countries. Screening of HLA-B*15:02 may help patients to prevent the occurrence of CBZ-induced TEN/SJS, especially in populations with a higher (≥5%) risk allele frequency.

Keywords: Carbamazepine, human leukocyte antigen-B*15:02, hypersensitivity, meta-analysis, screening

INTRODUCTION

Carbamazepine (CBZ) has been one of the most common causes of life-threatening severe adverse drug reactions, such as toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) in the world in recent years.[1-5] Furthermore, CBZ has commonly been reported to be associated with severe cutaneous adverse reactions (SCARs), including acute generalized exanthematous pustulosis and drug reaction with eosinophilia and systemic symptoms in addition to TEN and SJS.[6-8]

The human leukocyte antigen (HLA) B allele HLA-B*15:02 has been reported to be a potential genetic marker for CBZ-induced SCAR, including TEN and SJS.[1-3,5]

Moreover, the role of HLA-B*15:02 test screening and prevention of TEN/SJS has been the subject of longitudinal and cross-sectional studies.[9,10] However, the results of these studies have varied in different populations.

In general, CBZ is well tolerated. Although CBZ-induced SCAR is rare (the risk is estimated to be 10% in CBZ users),[11] the severity of SCAR cases caused by CBZ is high, with a mortality rates <5% for SJS and >30% for TEN, with sepsis being the most frequent cause of death.[11] Coinciding with a rise in the prevalence of gout is a global increase in the number of prescriptions for CBZ. Moreover, in recent years, CBZ has become the most common cause of TEN/SJS in many countries,[2,3,5,7] overtaking other well-known drugs associated

with such reactions, including allopurinol, phenytoin, and sulfonamides.[12-14] Although the incidence of TEN and SJS is low (0.4–6.0 cases per million person-years in the general Chinese population), they are severe life-threatening adverse drug reactions with mortality rates as high as 5%–12.5% for SJS and 50% for TEN.[11]

HLA alleles are major susceptible genes for drug hypersensitivity.[15,16] HLA-B plays an important role in how the immune system recognizes and responds to pathogens. In separate studies from 2004 to 2005, Hung *et al.* reported that in Han Chinese patients in Taiwan, there was a strong association between CBZ- and allopurinol-induced TEN/SJS and the HLA-B*15:02 and HLA-B*58:01 alleles,[17] respectively. Other studies have also revealed a strong association

between HLA-B*15:02 and CBZ-induced TEN/SJS in Han Chinese,[5] Thai,[2] and Korean populations.[3,7] In subsequent studies, a strong association between CBZ-induced SCAR and HLA-B*15:02 was observed in several Han Chinese populations with high frequencies of this allele (94.11%),[5,18-20] whereas interestingly, studies in some Asian populations, such as in Japanese[21,22] and Europeans,[23,24] did not find any association between HLA-B*15:02 and CBZ-induced cutaneous ADRs. However, the degree of the association between HLA-B*15:02 and CBZ-induced SCAR and its clinical significance remain uncertain in other populations. The aim of the current study was to systematically review the association between the HLA-B*15:02 allele and CBZ-induced TEN/SJS in different populations. We also investigated the diagnostic performance and clinical utility of HLA-B*15:02 testing for the prevention of TEN/SJS in general populations who have either a high or low frequency of this allele.

MATERIALS AND METHODS

A comprehensive search of peer-reviewed articles indexed in the electronic databases of PubMed, EMBASE, and Ovid Medline was performed, and the reference lists of the retrieved articles were also reviewed to identify additional studies for inclusion.

The time frame for the electronic search was from January 2000 to December 2017 with no language restriction. Moreover, we reviewed the reference lists of several previously published reviews on HLA-B*15:02 testing. Search terms included "human leukocyte antigen," "HLA-B*15:02," "carbamazepine," "hypersensitivity," "screening," "sensitivity," "specificity," "predictive value," and "likelihood ratio."

When multiple articles for a single study had been published by the same teams or authors, we used the most relevant publication and supplemented it, if necessary, with data from the authors' other publications. Authors of studies were contacted when pertinent information was not available in the published version.

The quality of each included study was evaluated according to the Quality Assessment of Studies of Diagnostic Accuracy-2 (QUADAS-2).[25] Data were pooled by means of a random-effects model, and then, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive and negative likelihood ratios (LR+ and LR−), diagnostic odds ratios (DOR), summary receiver operating characteristic (SROC) curve, and 95% confidence intervals (CI) were calculated.[26] Heterogeneity across studies was assessed through the I^2 statistic. An I^2 statistic >50% was considered substantial heterogeneity.[26] If substantial heterogeneity existed, subgroup analyses would be conducted to explore the heterogeneity.[27] The primary analyses were based on population control studies. The primary outcomes were CBZ-induced TEN and SJS. The analyses were also performed separately on studies using different control groups (e.g., CBZ-treated control patients [CBZ-tolerant matched-control studies]).

Subgroup analyses by race/ethnicity were also performed to determine the robustness of the findings.

RESULTS

Characteristics of the study populations

In the present study, we identified 201 articles from online databases, of which 126 irrelevant articles were excluded from the study. The remaining 75 articles were further assessed for eligibility, and 26 articles were finally included in the meta-analysis, consisting of a total of 4785 patients [Supplementary Table 1].

The quality of the included studies as assessed by the QUADAS-2 tool was generally high, with all studies meeting eight or more of the criteria.

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for studies retrieved through the electronic search and the selection processes for study inclusion.

Specifically, the studies included 373 TEN/SJS cases, 804 CBZ-tolerant matched-control subjects, and 3452 general population control subjects. The detailed characteristics of each study are presented in Supplementary Table 1.

Analysis of population control and carbamazepine-tolerant matched-control studies

The diagnostic indicators and frequencies of the HLA-B*15:02 allele in all the included studies are shown in Supplementary
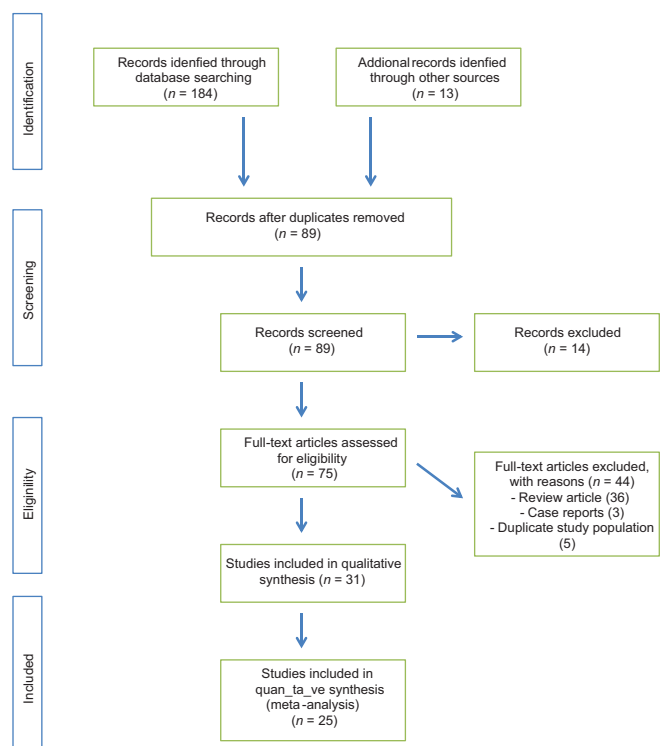
Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for studies retrieved through the electronic search and the selection processes

Table 2. In the population control studies (total n = 3452), the overall mean sensitivity of HLA-B*15:02 was 62.17% (range: 25%–99%), specificity was 95.4% (80.8%–100%), PPV was 68.30% (16.7%–100%), NPV was 89.97% (76%–99.9%), LR+ was 39.45 (2.14–183.56), LR− was 0.39 (0.07–0.76), and the DOR was 256.52 (2.6–2504.71) [Supplementary Table 2]. The corresponding data from the CBZ-tolerant matched-control studies (total n = 804) were sensitivity, 58.98% (28.3%–99%); specificity, 90.77% (66.7%–99.4%); PPV, 63.88% (16.7%–95%); NPV, 90.34% (78.6%–99.4%); LR+, 32.94 (0.86–81.94); LR−, 0.46 (0.01–1.07); and DOR, 154 (0.8–895.24). Figure 2 shows the HLA-B*15:02 allele frequencies of the general populations and their associations with CBZ-induced TEN/SJS in each of the ethnic groups of the included studies.

Figure 2 shows the geographical distribution and frequencies of HLA-B*15:02 in different ethnic general populations with a >5% allele frequency.

Statistical pooling of outcomes

All study diagnostic indicators were pooled from the included studies, including sensitivity, specificity, LR+, LR−, DOR, and SROC. In the population control studies, the pooled sensitivity, specificity, LR+, LR−, DOR, and area under the SROC curve were 0.67 (95% CI = 0.63–0.72), 0.98 (95% CI = 0.98–0.99), 19.73 (95% CI = 10.54–36.92), 0.34 (95% CI = 0.23–0.49), 71.38 (95% CI = 34.89–146.05), and 0.96 (95% CI = 0.92–0.98), respectively. Summaries of the pooled diagnostic indicators for the population control studies are shown in Supplementary Table 3 and graphically in Figure 3.

In the CBZ-tolerant matched-control studies, the corresponding pooled sensitivity, specificity, LR+, LR−, DOR, and area under the SROC curve were 0.67 (95% CI = 0.63–0.71), 0.98 (95% CI = 0.98–0.99), 19.72 (95% CI = 10.54–36.92), 0.34 (95% CI = 0.23–0.49), 71.38 (95% CI = 34.89–146.05), and 0.95 (95% CI = 0.90–0.98), respectively.

Subgroup analysis

In the meta-analysis, it was revealed that there was considerable heterogeneity (I^2 > 50%) for all statistical
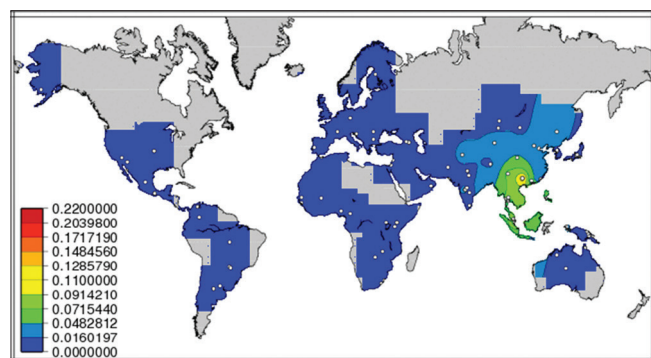
Figure 2: Geographical distribution and frequencies of human leukocyte antigen-B*15:02 in different ethnic general populations

measures except for the DOR, which had an I^2 = 51.6% [Supplementary Table 3a-e]. TEN/SJS cases were found to be significantly associated with HLA-B*15:02 allele frequencies in both population control (DOR 71.39, 95% CI = 34.90–146.05, P < 0.005) and CBZ-tolerant matched-control studies (DOR 43.84, 95% CI = 11.13–172.58, P < 0.005). Since a common effect size was shared among population control and matched-control studies and significant heterogeneity existed, a random-effects model was used and subgroup analyses were performed.

Subgroup analyses for Han Chinese, Thai, and Malaysian populations yielded similar findings. Specifically, racial/ethnic subgroup analyses revealed similar findings with respect to DOR for Han Chinese (99.28; 95% CI = 22.20–443.88), Thai (61.01; 95% CI = 23.05–161.44), and Malaysian (30; 95% CI = 7.08–126.68) populations, which are similar to the pooled DOR for the relationship between the HLA-B*15:02 allele and CBZ-induced TEN/SJS across all populations (71.38; 95% CI = 34.89–146.05). Vietnamese and Hindu populations were only accounted for in one study and thus were excluded from the combined analysis.

DISCUSSION

Association of human leukocyte antigen-B*15:02 and carbamazepine-induced toxic epidermal necrolysis/Stevens–Johnson syndrome across different populations

CBZ is widely used to treat epilepsy, bipolar disorder, trigeminal neuralgia, and chronic pain.[43] However, some patients develop adverse hypersensitivity reactions, ranging from mild skin rashes to life-threatening SCAR, including TEN and SJS.[14,15]

The identification of genetic markers that predispose individuals to the development of CBZ-induced TEN/SJS offers the possibility of those with such susceptibilities to avoid this drug.[36] However, there is no agreed-upon international guideline for HLA-B*15:02 screening before patients are treated with CBZ; US FDA has issued a black box warning for the physicians to test the allele before the initiation of carbamazepine.[11] In the present study, we found a strong association between HLA-B*15:02 and CBZ-induced TEN/SJS across different ethnic populations.[5,21,29-41] Given that CBZ-induced TEN/SJS has serious life-threatening consequences and has long-term sequelae after development, such as blindness and corneal opacity, and that there are available drug alternatives to CBZ, testing for HLA-B*15:02 before CBZ initiation may be valuable and justifiable to prevent TEN/SJS caused by CBZ.

In the present study, we investigated the diagnostic performance and clinical utility of HLA-B*15:02 testing for the prevention of TEN/SJS in general populations who have either a high (≥5%–10%) or low (<1%–5%) HLA-B*15:02 allelic frequency. Our results revealed that there was a strong relationship between the HLA-B*15:02 allele and CBZ-induced TEN/SJS in Han Chinese,[5,15,19,28,33] Thai,[2]
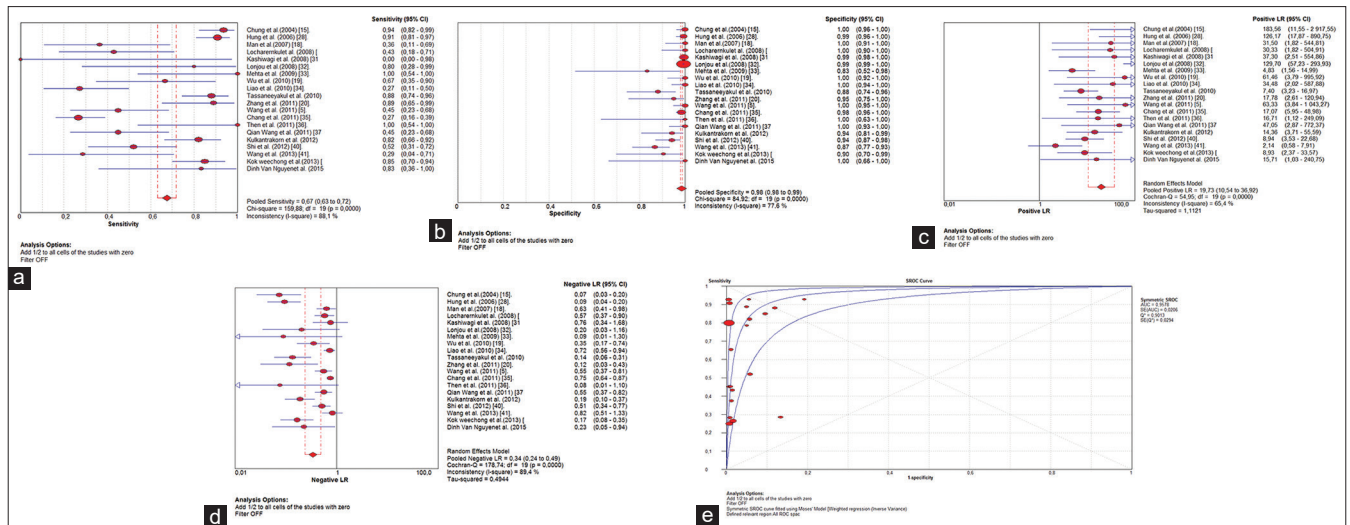
Figure 3: Graphical representations of the pooled diagnostic indicators for the diagnosis of toxic epidermal necrolysis and Stevens–Johnson syndrome through human leukocyte antigen-B*15:02 testing. Shown are sensitivity (a), specificity (b), positive likelihood ratio (c), negative likelihood ratio (d), and summary receiver operating characteristic curve (e)

and Korean.[3,7] Overall, the pooled DOR for the relationship between the HLA-B*15:02 allele and CBZ-induced TEN/SJS in the population control studies was 71.38 (95% CI = 34.89–146.05) with homogeneity across all populations (I^2 statistic = 51.6%), which is similar to a previous systematic review (DOR: 113.4 [95% (CI) = 51.2–251.0], $P < 1 \times 10^{-5}$).[44] Moreover, subgroup analyses of studies on Asian (including Han Chinese, Thai, and Korean), Malaysian, and Thai populations revealed similar findings for Han Chinese (99.28; 95% CI = 22.20–443.88), Thai (61.01; 95% CI = 23.05–161.44), and Malaysian (30; 95% CI = 7.08–126.68) populations. However, there were no relevant HLA-B*15:02 tests and associated CBZ studies from America, India, or Africa. Mehta *et al.* reported the association of HLA-B*15:02 allele and CBZ-induced SJS/TEN in Indian population.[32] Another Indian study done in North Indian population observed an association between HLA-B*15:02 allele and CBZ-induced SJS/TEN.[45] A study done in Indian population in Malaysia, most of whom were of South Indian origin, also showed a strong association of HLA-B*15:02 allele and CBZ-induced SJS/TEN.[46]

The increased risk of Severe Carbamazepine Hypersensitivity Syndrome in in the Chinese population stems from the higher frequency of the HLA-B*15:02 allele in this populations (allelic frequency ≥5% from the dbMHC database).[47]

In the included studies herein, the overall pooled sensitivity and specificity of HLA-B*15:02 for detecting CBZ-induced TEN/SJS were 67% (95% CI = 63%–72%) and 98% (95% CI = 98%–99%), respectively [Supplementary Table 2]. Moreover, in the present study, we found that HLA-B*15:02 testing had a high NPV (mean 68.30% with a range of 6.3%–100%) in the prevention of CBZ-induced TEN/SJS across all of the included populations, indicating that HLA-B*15:02 testing may be a valuable means of preventing SCAR associated with CBZ use. Furthermore, it was observed that the PPV

(mean: 63.88%, median: 88.45%, and range: 16.7–95%); LR+, 32.94 (0.86–81.94); and LR−, 0.46 (0.01–1.07) of HLA-B*15:02 testing varied with the prevalence (pretest probability) of TEN/SJS and HLA-B*15:02 allele frequency, whereas there was no significant change in the NPV with changes in TEN/SJS prevalence or HLA-B*15:02 allele frequency.

In real-world clinical practice, the estimated low PPV (3%)[48] of HLA-B*15:02 testing is not of great concern because physicians would not intend to use CBZ in patients who are HLA-B*15:02 positive. Moreover, the aim of a screening test for drug hypersensitivity reactions is to have a high sensitivity and a high NPV. The optimal implementation of HLA-B*15:02 screening at this time is as an initial diagnostic test that offers significant arguments against CBZ-induced TEN/SJS if negative, as well as supportive information on the development of CBZ-induced TEN/SJS if positive, especially in those populations with a higher (≥5%) allele frequency. CBZ-induced TEN and SJS remain a life-threatening problem. In clinical practice, the incidence of SCAR in CBZ using patients was estimated to be 0.1%–0.4% in different ethnic populations[5,21,29-41] including Han Chinese,[5] Thai,[2] and Korean populations.[3,7]

Carbamazepine is the leading cause of drug-induced toxic epidermal necrolysis/Stevens–Johnson syndrome in many countries

As previously mentioned, CBZ has been reported as one of the most common causes of SCAR,[1-3,5] especially TEN/SJS,[5,21,29-41] in many different countries. Through a review of the literature, we found that the leading cause of SCAR in many regions/countries, including Han Chinese,[5] Thai,[2] and Korean populations,[3,7] has been reported to be CBZ. In contrast to previous studies, Huang *et al.*[49] found CBZ to be the most common single drug associated with cutaneous adverse drug reactions, followed by allopurinol and antibiotics. This observation is compatible to experiences in Taiwan

where CBZ was the leading cause of TEN/SJS and SCAR in the last decade.[50] In a previous study, data from surveillance networks in France, Germany, Italy, and Portugal from 1989 to 1993 revealed that the use of antibacterial sulfonamides, anticonvulsant agents (CBZ), nonsteroidal anti-inflammatory drugs (oxicam), and allopurinol was associated with a large increase in the risk of TEN and SJS.[14]

Genetic and clinical factors associated with carbamazepine-induced toxic epidermal necrolysis/Stevens–Johnson syndrome

To date, the pathogenesis of TEN and SJS is still not completely understood. The proteins encoded by the HLA genes located on the major histocompatibility complex (MHC) region of the human chromosome 6p21.3 play a central role in immune reactions by presenting antigens to T-cell receptors.[51] The strong associations between HLA-B*15:02 and CBZ-induced TEN/SJS suggest that genetic predisposition plays an important role in the pathogenesis of TEN/SJS.

It is not clear why only 3%[48] of HLA-B*15:02-positive patients developed SCAR after taking CBZ, which suggests that other factors may also be involved in mediating the increased risk.[12] Although the precise mechanisms involved in SCAR development and TEN/SJS are still unclear, several different factors have been postulated in their pathogenesis,[52,53] which have mainly included those related to cell-mediated immunity directed to CBZ, in addition to viruses, genetic factors, and metabolic pathways.[5,21,29-41]

Cutaneous drug reactions may be caused by several different mechanisms.[14] TEN and SJS are characterized by massive keratinocyte apoptosis.[14]

Wei *et al*. suggested that the endogenous peptide-loaded HLA-B*15:02 molecule presented CBZ to cytotoxic T lymphocytes (CTLs) without the involvement of intracellular drug metabolism or antigen processing. The HLA-B*15:02/peptide/β2-microglobulin protein complex showed binding affinity toward chemicals sharing 5-carboxamide on the tricyclic ring, as with CBZ. However, modifications of the ring structure of CBZ altered HLA-B*15:02 binding and CTL response. In addition to HLA-B*15:02, other HLA-B*75 family members could also present CBZ to activate CTLs, whereas members of the HLA-B*62 and HLA-B*72 families could not. Three residues (Asn63, Ile95, and Leu156) in the peptide-binding groove of HLA-B*15:02 were involved in CBZ presentation and CTL activation. In particular, Asn63 shared by members of the B*75 family was the key residue. Computer simulations revealed a preferred molecular conformation of the 5-carboxamide group of CBZ and the side chain of Arg62 on the B pocket of HLA-B*15:02.[54] In addition, other genetic and clinical factors may influence a patient's risk of CBZ-induced adverse reactions. However, given our current knowledge regarding CBZ-induced TEN/SJS, HLA-B*15:02 testing is beneficial in clinical practice for patients who are about to initiate CBZ, especially for those from ethnic backgrounds with a higher (≥5%) risk

allele frequency [Figure 4]. Particularly, these patients should be advised about the availability of such a test so that they can choose to be genotyped if they have concerns about TEN/SJS, which can be potentially life threatening. Moreover, it should be noted that the risk of developing CBZ-induced TEN/SJS is the highest in the first 3 months of drug treatment,[55] whereas the risk of TEN/SJS is very low for patients who have already been treated with CBZ for more than 3 months and thus generally do not require testing. Therefore, there is an urgency to better understand the mechanisms and factors that predispose individuals to CBZ-induced SCAR and TEN/SJS. The higher rates of TEN/SJS in Asians are likely related to the high frequency of the HLA-B*15:02 allele in Asian populations compared to that in other ethnicities. Comprehensive lists of HLA-B*15:02 frequencies by ethnicity are available elsewhere and are summarized as follows: Australia, 15.6%; Cape York, 15%; Europe, 5.8%; Croatian, 7%; Cuban, 4.3%; North America, 7.5%; North Africa, 3.3%; Brazilian, 7.6%; Han Chinese, 11.7%; New Delhi, 3%; Sub-Saharan Africa, 14.6%; Ugandan, 13.1%; and Zambian, 13.6% [Figure 2].[47]

It is interesting to note that the strength of genetic associations that have been found directly relates to the prevalence of the susceptibility allele in the different ethnic populations with consistent results reported from Southeast and South Asia, Thailand, and Korea where the frequencies of the risk alleles are high (≥5%). Given that HLA-B*15:02 testing has a very high specificity and high NPV, it is apparent that over 99% of CBZ-induced TEN/SJS is preventable through pretreatment screening in those populations with a reasonably high carrier rate (i.e., high-risk subpopulations) of the HLA-B*15:02 allele.

Our systematic meta-analysis focused only on the relationship between the HLA-B*15:02 allele and CBZ-induced SJS and TEN. Other genes that may be associated with SJS and TEN (such as HLA-A*31:01) were excluded from our study.[56]

In summary, there are no compelling data to show that two HLA alleles predispose to different forms of CBZ hypersensitivity. One of these tests, HLA-B*15:02, is already used in Asian countries before the initiation of CBZ therapy. HLA-A*31:01 has been more recently identified, and whether the test is adopted by clinicians and the drug label changed by regulators are unclear at present. However, given that the test characteristics are comparable to those for HLA-B*1502, we are in favor of a label change. Additional work – specifically, further studies to determine the causal pathways that may help in improving the test characteristics – is needed. Different ethnic
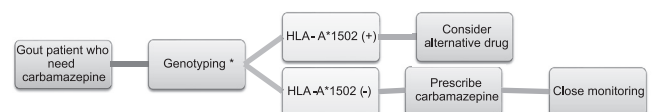
Figure 4: Recommendation for carbamazepine prescription in patients. *Genotyping by molecular biology or flow cytometry especially in countries where human leukocyte antigen-B*15:02 is highly expressed (>5%) in the general population

populations should also be studied for the association between CBZ hypersensitivity and HLA allele frequencies. Moreover, whether these tests are applicable for other phenotypes, for example, liver injury; whether HLA-A*31:01 also predisposes to hypersensitivity reactions with other antiepileptic drugs; and whether testing is cost-effective and acceptable among clinicians and patients still needs to be determined.

Conclusions

We found a strong relationship between HLA-B*15:02 and CBZ-induced SJS and TEN in Han Chinese, Thai, and Malaysian populations. The recognition of HLA-B allele status before initiation of the drug may be beneficial to some groups of patients. Such information will assist physicians in determining the optimal drug therapy.

What is known about this topic

The clinical features of CBZ hypersensitivity suggest an immune-mediated etiology, and the discovery of drug-specific T-cells in hypersensitive individuals is consistent with this hypothesis. HLAs play a central role in the immune response to antigens, and it has been hypothesized that specific HLA molecules may present a drug or its metabolites to specific T-cells, which subsequently triggers an immune response. This has been borne out by studies that have shown strong associations with two HLA alleles, particularly HLA-B*15:02, which was first reported in Han Chinese patients, and HLA-A*31:01, which has been reported in Japanese and Caucasian populations.

What this study adds

We found a strong relationship between HLA-B*15:02 and CBZ-induced SJS and TEN in Han Chinese, Thai, and Malaysian populations. Screening of HLA-B*15:02 may help patients to prevent the occurrence of CBZ-induced TEN/SJS, especially in populations with a higher (≥5%) risk allele frequency.

Acknowledgments

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Characteristics of the studies included in the meta-analysis

Author	Publication year	Country	Population	TEN/SJS[‡]	Control[‡]
Population control					
Chung et al., 2004[15]	2004	Taiwan	Chinese	44/44	3/101
Hung et al., 2006[28]	2006	Taiwan	Chinese	59/60	6/144
Alfirevic et al., 2006[24]	2006	UK	Caucasian	0/2	0/43
Man et al., 2007[18]	2007	Hong Kong	Chinese	4/4	7/48
Locharernkul et al., 2008[29]	2008	Thailand	Thai	6/6	8/42
Kaniwa et al., 2008[30]	2008	Japan	Japanese	0/7	0/493
Kashiwagi et al., 2008[21]	2008	Japan	Japanese	0/2	1/371
Lonjou et al., 2008[31]	2008	France	Caucasian	4/12	1/1290
Mehta et al., 2009[32]	2009	India	Hindu	6/8	0/10
Wu et al., 2010[19]	2010	China	Chinese	8/8	4/50
Liao et al., 2009[33]	2010	China	Chinese	6/6	16/76
Tassaneeyakul et al., 2010[2]	2010	Thailand	Thai	37/42	5/42
Zhang et al., 2011[20]	2011	China	Chinese	16/17	2/21
Wang et al., 2011[5]	2011	China	Chinese	9/9	11/80
Chang et al., 2011[34]	2011	Malaysia	Malaysian	17/21	47/300
Then et al., 2011[35]	2011	Malaysia	Malaysian	6/6	0/8
Wang et al., 2011[5]	2011	China	Chinese	9/9	11/62
Kulkantrakorn et al., 2012[36]	2012	Thailand	Thai	32/34	7/40
Niihara et al., 2012[37]	2012	Japan	Japanese	0/3	0/33
Shi et al., 2012[38]	2012	Asian	Chinese	13/18	12/93
Wang et al., 2013[39]	2013	China	Chinese	2/12	5/70
Chong et al., 2013[40]	2017	China	Chinese	5/5	1/10
Nguyen et al., 2015[41]	2015	Vietnam	Vietnamese	34/38	6/25
Subtotal				317/373	153/3452
Tolerant control					
Chung et al., 2004[15]	2004	Taiwan	Chinese	44/44	8/93
Wu et al., 2010[19]	2010	China	Chinese	8/8	6/71
Liao et al., 2009[33]	2010	China	Chinese	6/6	16/76
Zhang et al., 2011[20]	2011	China	Chinese	16/17	17/185
Wang et al., 2011[5]	2011	China	Chinese	9/9	11/62
Wang et al., 2011[5]	2011	China	Chinese	9/9	11/80
Kim et al., 2011[3]	2011	Korea	Koreans	1/7	0/50
He et al., 2013[42]	2014	China	Chinese	8/35	2/125
Wang et al., 2013[39]	2013	China	Chinese	2/12	5/25
Ritu Aggarwal et al., 2014	2014	India	Indian	2/9	0/37
Subtotal				105/156	76/804

[‡]Number positive for human leukocyte antigen-B*1502/total. TEN/SJS, TEN, and SJS. TEN=Toxic epidermal necrolysis; SJS: Stevens-Johnson syndrome

Supplementary Table 2: Diagnostic indicators of the included studies for the diagnosis of toxic epidermal necrolysis/Stevens-Johnson syndrome through human leukocyte antigen-B*1502 genetic testing

Author	TEN/SJS[†]	Control[†]	TP	FP	FN	TN	Sensitivity	Specificities	PPV	NPV	LR+	LR−	DOR
Population control													
Chung et al., 2004[15]	44/44	3/101	44	0	3	98	93.6	100	100	97	183.56	0.07	2504.71
Hung et al., 2006[28]	59/60	6/144	59	1	6	138	90.8	99.3	98.3	95.8	126.17	0.09	1357
Alfirevic et al., 2006[24]	0/2	0/43	0	2	0	43	50	94.6	16.7	98.9	9.20	0.53	17.40
Man et al., 2007[18]	4/4	7/48	4	0	7	41	37.5	98.9	90	84.7	31.5	0.63	49.80
Locharernkul et al., 2008[29]	6/6	8/42	6	0	8	34	43.3	98.6	92.9	80.2	30.33	0.57	52.76
Kaniwa et al., 2008[30]	0/7	0/493	0	7	0	493	50	98.5	6.3	99.9	33.40	0.51	65.80
Kashiwagi et al., 2008[21]	0/2	1/371	0	2	1	370	25	99.3	16.7	99.6	37.30	0.76	49.40
Lonjou et al., 2008[31]	4/12	1/1290	4	8	1	1289	80	99.4	33.3	99.9	129.70	0.20	644.50
Mehta et al., 2009[32]	6/8	0/10	6	2	0	10	92.9	80.8	72.2	95.5	4.83	0.09	54.60
Wu et al., 2010[19]	8/8	4/50	8	0	4	46	65.4	99	94.4	91.2	61.46	0.35	175.67
Liao et al., 2009[33]	6/6	16/76	6	0	16	60	28.3	99.2	93	78.6	34.48	0.72	47.67
Tassaneeyakul et al., 2010[2]	37/42	5/42	37	5	5	37	88.1	88.1	88.1	88.1	7.40	0.14	54.76
Zhang et al., 2011[20]	16/17	2/21	16	1	2	19	99	95	94.1	90.5	17.78	0.12	152
Wang et al., 2011[5]	9/9	11/80	9	0	11	69	45.2	99.3	95	85.8	63.33	0.55	114.83
Chang et al., 2011[34]	17/21	47/300	17	4	47	253	26.6	98.4	81	84.3	17.07	0.75	22.88
Then et al., 2011[35]	6/6	0/8	6	0	0	8	92.9	94.4	92.9	94.4	16.71	0.08	221
Wang et al., 2011[5]	9/9	11/62	9	0	11	51	45.2	99	95	81.7	47.05	0.55	85.09
Kulkantrakorn et al., 2012[36]	32/34	7/40	32	2	7	33	82.1	94.3	94.1	82.5	14.36	0.19	75.43
Niihara et al., 2012[37]	0/3	0/33	0	3	0	33	50	91.8	14.3	98.5	6.08	0.54	11.17
Shi et al., 2012[38]	13/18	12/93	13	5	12	81	52	94.2	72,2	87.1	8.94	0.51	17.55
Wang et al., 2013[39]	2/12	5/70	2	10	5	65	28.6	86.7	16.7	92.9	2.14	0.82	2.60
Chong et al., 2013[40]	34/38	6/25	34	2	6	19	85	90.5	94.4	76	8.93	0.17	53.83
Nguyen et al., 2015[41]	5/5	1/10	5	0	1	9	78.6	95	91.7	86.4	15.71	0.23	69.67
Tolerant control													
Chung et al., 2004[15]	44/44	8/93	44	8	0	85	99	91	84	99.4	10.94	0.01	895.24
Wu et al., 2010[19]	8/8	6/71	8	0	6	65	56.7	99.2	94.4	91	74.8	0.44	171.31
Liao et al., 2009[33]	6/6	16/76	6	0	16	60	28.3	99.2	92.9	78.6	34.48	0.72	47.67
Zhang et al., 2011[20]	16/17	17/185	16	1	17	168	48.5	99.4	94.1	90.8	81.94	0.52	158.12
Wang et al., 2011[5]	9/9	11/62	9	0	11	51	45.2	99	95	81.7	47.05	0.55	85.09
Wang et al., 2011[5]	9/9	11/80	9	0	11	69	45.2	99.3	95	85.8	63.33	0.55	114.83
Kim et al., 2011[3]	1/7	0/50	1	6	0	50	75	88.6	18.8	99	6.58	0.28	23.31
He et al., 2013[42]	8/35	2/125	8	27	2	123	80	82	22.9	98.4	4.44	0.24	18.22
Wang et al., 2013[39]	2/12	5/25	2	10	5	20	28.6	66.7	16.7	80	0.86	1.07	0.80
Ritu Aggarwal et al., 2014	2/9	0/37	2	7	0	37	83.3	83.3	25	98.7	5	0.2	25

TP=True positive, FP=False positive, FN=False negative, TN=True negative, PPV=Positive predictive value, NPV=Negative predictive value, LR+=Positive likelihood ratios; LR−=Negative likelihood ratio, DOR=Diagnostic odds ratio

Supplementary Table 3a: Summary of sensitivities (random-effects model)[†]

Study	Sensitivity	95% CI	TP/(TP + FN)	TN/(TN + FP)
Chung *et al.*, 2004	0.936	0.825-0.987	44/47	98/98
Hung *et al.*, 2006	0.908	0.810-0.965	59/65	138/139
Man *et al.*, 2007	0.364	0.109-0.692	4/11	41/41
Locharernkul *et al.*, 2008	0.429	0.177-0.711	6/14	34/34
Kashiwagi *et al.*, 2008	0.000	0.000-0.975	0/1	370/372
Lonjou *et al.*, 2008	0.800	0.284-0.995	4/5	1289/1297
Mehta *et al.*, 2009	1.000	0.541-1.000	6/6	10/12
Wu *et al.*, 2010	0.667	0.349-0.901	8/12	46/46
Liao *et al.*, 2010	0.273	0.107-0.502	6/22	60/60
Tassaneeyakul *et al.*, 2010	0.881	0.744-0.960	37/42	37/42
Zhang *et al.*, 2011	0.889	0.653-0.986	16/18	19/20
Wang *et al.*, 2011	0.450	0.231-0.685	9/20	69/69
Chang *et al.*, 2011	0.266	0.163-0.391	17/64	253/257
Then *et al.*, 2011	1.000	0.541-1.000	6/6	8/8
Qiam wang *et al.*, 2011	0.450	0.231-0.685	9/20	51/51
Kulkantrakorn *et al.*, 2012	0.821	0.665-0.925	32/39	33/35
Shi *et al.*, 2012	0.520	0.313-0.722	13/25	81/86
Wung *et al.*, 2013	0.286	0.037-0.710	2/7	65/75
Kok weechong *et al.*, 2013	0.850	0.702-0.943	34/40	19/21
Dinh Van Nguyen *et al.*, 2015	0.833	0.359-0.996	5/6	9/9

[†]Heterogeneity V^2=159.88 (df 19) P=0.000; inconsistency (I^2)=88.1%. TP=True positive, FP=False positive, FN=False negative, TN=True negative, CI=Confidence interval

Supplementary Table 3b: Summary of specificities (random-effects model)[‡]

Study	Specificities	95% CI	TP/(TP + FN)	TN/(TN + FP)
Chung *et al.*, 2004	1.000	0.963-1.000	44/47	98/98
Hung *et al.*, 2006	0.993	0.961-1.000	59/65	138/139
Man *et al.*, 2007	1.000	0.914-1.000	4/11	41/41
Locharernkul *et al.*	1.000	0.897-1.000	6/14	34/34
Kashiwagi *et al.*, 2008	0.995	0.981-0.999	0/1	370/372
Lonjou *et al.*, 2008	0.994	0.988-0.997	4/5	1289/1297
Mehta *et al.*, 2009	0.833	0.516-0.979	6/6	10/12
Wu *et al.*, 2010	1.000	0.923-1.000	8/12	46/46
Liao *et al.*, 2010	1.000	0.940-1.000	6/22	60/60
Tassaneeyakul *et al.*	0.881	0.744-0.960	37/42	37/42
Zhang *et al.*, 2011	0.950	0.751-0.999	16/18	19/20
Wang *et al.*, 2011	1.000	0.948-1.000	9/20	69/69
Chang *et al.*, 2011	0.984	0.961-0.996	17/64	253/257
Then *et al.*, 2011	1.000	0.631-1.000	6/6	8/8
Qiamwang *et al.*	1.000	0.930-1.000	9/20	51/51
Kulkantrakorn *et al.*	0.943	0.808-0.993	32/39	33/35
Shi *et al.*, 2012	0.942	0.870-0.981	13/25	81/86
Wung *et al.*, 2013	0.867	0.768-0.934	2/7	65/75
Dinh van nguyen *et al.*	0.905	0.696-0.988	34/40	19/21
Kok weechong *et al.*	1.000	0.664-1.000	5/6	9/9

[‡]Heterogeneity V^2=84.92 (df=19) P=0.000; inconsistency (I^2)=77.6%. TP=True positive, FP=False positive, FN=False negative, TN=True negative, CI=Confidence interval

Supplementary Table 3c: Summary of positive likelihood ratios (random-effects model)[§]

Study	LR+	95% CI	Percentage weight
Chung *et al.*, 2004	183.56	11.549-2917.6	3.30
Hung *et al.*, 2006	126.17	17.871-890.75	4.86
Man *et al.*, 2007	31.500	1.821-544.81	3.17
Locharernkul *et al.*	30.333	1.822-504.91	3.23
Kashiwagi *et al.*, 2008	37.300	2.507-554.86	3.40
Lonjou *et al.*, 2008	129.70	57.232-293.93	7.95
Mehta *et al.*, 2009	4.829	1.555-14.990	7.07
Wu *et al.*, 2010	61.462	3.793-995.92	3.27
Liao *et al.*, 2010	34.478	2.022-587.88	3.19
Tassaneeyakul *et al.*	7.400	3.226-16.974	7.92
Zhang *et al.*, 2011	17.778	2.613-120.94	4.94
Wang *et al.*, 2011	63.333	3.845-1043.3	3.24
Chang *et al.*, 2011	17.066	5.947-48.976	7.30
Then *et al.*, 2011	16.714	1.122-249.09	3.40
Qiamwang *et al.*	47.048	2.866-772.37	3.25
Kulkantrakorn *et al.*	14.359	3.709-55.595	6.44
Shi *et al.*, 2012	8.944	3.528-22.676	7.65
Wung *et al.*, 2013	2.143	0.581-7.908	6.57
Dinh van nguyen *et al.*	8.925	2.373-33.567	6.52
Kok weechong *et al.*	15.714	1.026-240.75	3.35

[§]Heterogeneity V^2=54.95 (df=19) P=0.000; inconsistency (I^2)=65.4%.
LR+=Positive likelihood ratios, CI=Confidence interval

Supplementary Table 3e: Summary diagnostic odds ratios (random-effects model)[††]

Study	DOR	95% CI	Percentage weight
Chung *et al.*, 2004	2504.7	126.68-49523.3	3.79
Hung *et al.*, 2006	1357.0	159.84-11520.5	5.57
Man *et al.*, 2007	49.800	2.422-1024.0	3.72
Locharernkul *et al.*	52.765	2.700-1031.3	3.80
Kashiwagi *et al.*, 2008	49.400	1.594-1531.1	3.12
Lonjou *et al.*, 2008	644.50	64.687-6421.4	5.17
Mehta *et al.*, 2009	54.600	2.248-1326.2	3.46
Wu *et al.*, 2010	175.67	8.643-3570.4	3.74
Liao *et al.*, 2010	47.667	2.552-890.46	3.88
Tassaneeyakul *et al.*	54.760	14.618-205.13	8.04
Zhang *et al.*, 2011	152.00	12.591-1834.9	4.73
Wang *et al.*, 2011	114.83	6.246-2110.9	3.91
Chang *et al.*, 2011	22.878	7.370-71.021	8.66
Then *et al.*, 2011	221.00	3.847-12694.8	2.44
Qiamwang *et al.*	85.087	4.613-1569.4	3.90
Kulkantrakorn *et al.*	75.429	14.559-390.79	6.98
Shi *et al.*, 2012	17.550	5.305-58.058	8.45
Wung *et al.*, 2013	2.600	0.443-15.262	6.60
Dinh van nguyen *et al.*	53.833	9.875-293.48	6.83
Kok weechong *et al.*	69.667	2.399-2022.8	3.21

[††]Heterogeneity V^2=39.22 (df=19) P=0.004; inconsistency (I^2)=51.6%.
CI=Confidence interval, DOR=Diagnostic odds ratio

Supplementary Table 3d: Summary of negative likelihood ratios (random-effects model)[¶]

Study	LR−	95% CI	Percentage weight
Chung *et al.*, 2004	0.073	0.027-0.201	4.49
Hung *et al.*, 2006	0.093	0.043-0.199	5.28
Man *et al.*, 2007	0.633	0.408-0.982	6.26
Locharernkul *et al.*	0.575	0.369-0.896	6.25
Kashiwagi *et al.*, 2008	0.755	0.339-1.681	5.16
Lonjou *et al.*, 2008	0.201	0.035-1.162	2.64
Mehta *et al.*, 2009	0.088	0.006-1.295	1.44
Wu *et al.*, 2010	0.350	0.166-0.739	5.33
Liao *et al.*, 2010|	0.723	0.559-0.936	6.67
Tassaneeyakul *et al.*	0.135	0.059-0.310	5.06
Zhang *et al.*, 2011	0.117	0.032-0.434	3.62
Wang *et al.*, 2011	0.552	0.374-0.814	6.39
Chang *et al.*, 2011	0.746	0.643-0.865	6.82
Then *et al.*, 2011	0.076	0.005-1.098	1.45
Qiamwang *et al.*	0.553	0.374-0.816	6.39
Kulkantrakorn *et al.*	0.190	0.097-0.374	5.56
Shi *et al.*, 2012	0.510	0.338-0.769	6.34
Wung *et al.*, 2013	0.824	0.512-1.328	6.16
Dinh van nguyen *et al.*	0.166	0.078-0.351	5.32
Kok weechong *et al.*	0.226	0.054-0.938	3.33

[¶]Heterogeneity V^2=179.74 (df=19) P=0.000; inconsistency (I^2)=89.4%.
CI=Confidence interval, LR−=Negative likelihood ratios