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HLA-B*57:01 confers genetic susceptibility to carbamazepine-induced SJS/TEN in Europeans

To the Editor,

Carbamazepine (CBZ) is a widely used antiepileptic drug for the treatment of epilepsy, as well as bipolar disorder, trigeminal neuralgia, etc. Although effective for treating neurological diseases, CBZ may cause cutaneous adverse reactions ranging from mild maculopapular exanthema (MPE) to life-threatening severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS). CBZ is known as one of the most common causative drugs for SCAR in different populations.¹

Stevens-Johnson syndrome/toxic epidermal necrolysis is characterized as epidermal detachment with high mortality rate ranging from 10%-50%.¹ HLA-B*15:02 was found to be strongly associated with CBZ-induced SJS/TEN in Han Chinese² and further validated in many populations, especially in countries of Southeast Asia, such as Thailand, Malaysia, Vietnam, India. Genetic screening of HLA-B*15:02 prior to the use of CBZ for patients with Southeast Asian ancestry is recommended by US FDA and related health administrations in many countries of the world. Furthermore, HLA-A*31:01 was reported to be associated with CBZ hypersensitivity reactions in Europeans.³ Our study revealed that HLA-A*31:01 is much more related to CBZ-induced MPE/DRESS than CBZ-SJS/TEN,⁴ which was confirmed by other studies.⁵ However, the genetic susceptibility of CBZ-SJS/TEN in Europeans remains unclear. Therefore, we conducted an international study to enroll patients with CBZ-SJS/TEN. We aimed to investigate the genetic predisposition of CBZ-SJS/TEN and further evaluate the strength of association for CBZ-SCAR in Europeans.

In total, we enrolled 31 patients with CBZ-SJS/TEN, including 17 patients with SJS, 10 with SJS/TEN overlap, and four with TEN from Europe. The phenotypes of SJS/TEN were clinically assessed using the diagnosis criteria for SJS/TEN of the RegiSCAR group.⁶ In a second independent step, causality assessment was performed in each case using the algorithm for assessment of drug causality in epidermal necrolysis, that is SJS/TEN (ALDEN).⁷ Only probable and definite cases of SJS/TEN and causality for CBZ (ALDEN score >4) were included for this study. Written informed consent was obtained from each participant. Among them, there are two Vietnamese from France and one Thai patient from Germany. The HLA-A and HLA-B data of patients with CBZ-SJS/TEN were determined by SeCore HLA sequence-based typing (Table S1).

To identify the HLA association of CBZ-SJS/TEN among people with European ancestry, we included Europeans (N = 28) for analysis (Table 1). Our result revealed that HLA-B*57:01 was strongly associated with CBZ-SJS/TEN in Europeans using either the dataset of "Central Europe general population controls"⁸ ($P_c = 1.83 \times 10^{-5}$) (Table 1 and Table S2), or "1000G EUR controls"⁹ ($P_c = 4.58 \times 10^{-4}$) (Table S3). HLA-B*57:01 allele was observed in 39.29% (11/28) of patients with CBZ-SJS/TEN, but only in 6.69% (593/8862) of European general population controls (OR = 9.0, 95% CI = 4.2-19.4; $P = 9.62 \times 10^{-7}$; $P_c = 1.83 \times 10^{-5}$) (Table 1 and Table S2). Other HLA alleles showed no association as their $P_c > 0.05$ (Table S2). By comparison, the two Vietnamese patients with CBZ-induced SJS/TEN carried the HLA-B*15:02 allele (Table S1).

We further analyzed the HLA associations in CBZ-SCAR by combining our previous data of 10 patients with CBZ-DRESS⁴ (Table 1, Table S4). HLA-A*31:01 shows significant association with CBZ-DRESS (present in 70% of patients, $P = 4.0 \times 10^{-8}$), but not with CBZ-SJS/TEN (Table 1). Furthermore, HLA-B*57:01 was absent in any European patient with CBZ-DRESS. HLA-B*57:01 or HLA-A*31:01 was present in 55.26% (21/38) of CBZ-SCAR patients, and only in 10.96% (971/8862) of European general population controls (OR = 10.0, 95% CI = 5.3-19.1; $P = 3.58 \times 10^{-11}$) (Table 1). To verify whether the HLA-B*57:01 protein interacts with CBZ, we generated the recombinant protein HLA-B/*2-microglobulin complex and performed Biacore T200 surface plasmon resonance (SPR) assay (see the methods described in Supporting Information). Our results revealed that CBZ interacts with HLA-B*57:01 in a concentration-dependent manner (Figure 1A). Furthermore, CBZ shows affinity to HLA-B*57:01 and HLA-B*15:02 proteins only, but not HLA-B*15:01 or HLA-B*51:01 proteins (Figure 1B).

Severe cutaneous adverse reactions are rare but life-threatening adverse reactions. The incidence of SJS/TEN is low, with 1-2 cases per million persons per year.² This report provides the evidence that HLA-B*57:01 is strongly associated with CBZ-SJS/TEN in Europeans ($P_c = 1.83 \times 10^{-5}$), but not with CBZ-DRESS in Europeans. We did not find a patient of Han Chinese origin with CBZ-SJS/TEN, who carried HLA-B*57:01 (data not shown). The frequencies of HLA-B*57:01 alleles are different among various ethnic groups. Current information from Allele Frequency Net Database (<http://www.allelefrequencies.net/>) revealed that HLA-B*57:01 is present in about 2.5%-8.9% of Europeans, 3.7%-6.2% of persons with European ancestry in the USA, 3%-5.5% of persons with European ancestry in Australia, and 2%-8% of Israelis, but is largely absent in Northeast and Southeast

Mockenhaupt, Wang and Hung are contributed equally to this work.

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TABLE 1 Association of HLA-B*57:01, HLA-A*31:01, and CBZ-induced SCAR in patients with European descent

Subgroup	SCAR case N (%)	General population N (%)	Odds ratio (95% CI)	P value	Sensitivity (%)	Specificity (%)
HLA-B*57:01						
CBZ-SJS/TEN	11/28 (39.29%)	593/8862 (6.69%)	9.0 (4.2-19.4)	9.62×10^{-7}	39.29	93.31
CBZ-DRESS*	0/10 (0%)	593/8862 (6.69%)	0.7 (0.0-11.3)	1	0	93.31
HLA-A*31:01						
CBZ-SJS/TEN	4/28 (14.29%)	396/8862 (4.52%)	3.6 (1.2-10.3)	0.035	14.29	95.48
CBZ-DRESS ^a	7/10 (70%)	396/8862 (4.52%)	49.9 (12.9-193.6)	4.0×10^{-8}	70.00	95.48
HLA-B*57:01 or A*31:01						
SCAR	21/38 (55.26%)	971/8862 (10.96%)	10.0 (5.3-19.1)	3.58×10^{-11}	55.26	89.04

Note: Only patients with European descent were included for HLA analysis.

^aThe detailed information of HLA-A*31:01 association with CBZ-DRESS was shown in Table S4 and adapted from our previous study.⁴

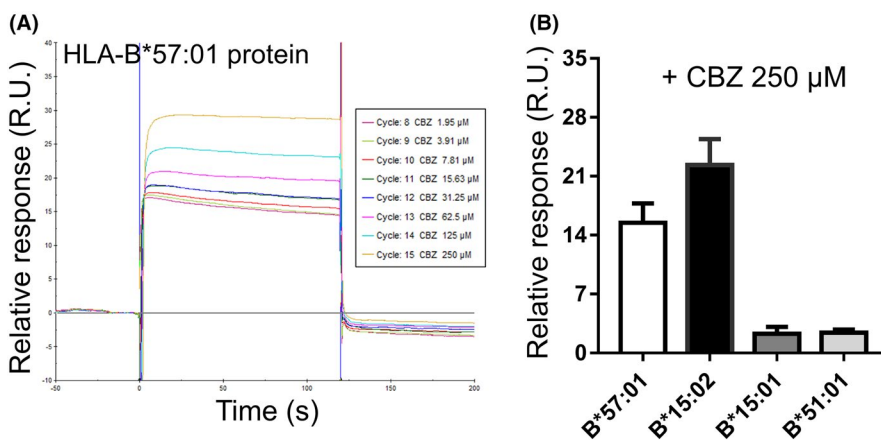


FIGURE 1 The interaction between HLA-B*57:01 protein and carbamazepine. (A) The interaction between HLA-B*57:01 protein and CBZ was analyzed by Biacore T200 surface plasmon resonance (SPR) assay (see methods described in Supplement Information). The binding response of CBZ to HLA-B*57:01 protein shows a concentration-dependent manner. (B) Binding response of HLA-B proteins to CBZ (250 μM) are shown

Asians (<0.5%). The European population is complicated in terms of genetic ancestry, and the population stratification of European populations is significant. In this study, our association study was not controlled for stratification effects, and our models are not appropriately controlled for these difference. Therefore, we used two datasets of European population controls,^{8,9} and both confirm that HLA-B*57:01 is significantly associated with CBZ-SJS/TEN in Europeans. The HLA-B*57:01 allele is also known to be strongly associated with abacavir hypersensitivity.⁸ The abacavir-HLA-B*57:01 interaction has been suggested as an altered peptide repertoire model, in which abacavir causes the conformational changes of endogenous peptides presented by HLA-B*57:01.⁹ We previously reported that CBZ can directly interact with HLA-B*15:02 protein without the involvement of antigen-processing pathways. CBZ-HLA-B*15:02 interaction is considered as the “pharmacological interaction with immune receptors (p-i)” model.¹⁰ Interestingly, in this study, we found that CBZ could also interact with HLA-B*57:01 protein by SPR assay. However, whether HLA-B*57:01 protein binds to CBZ and presents the drug epitope to activate immune response in CBZ-SJS/TEN needs further exploration.

The strong association between HLA-A*31:01 and CBZ-DRESS was observed in our previous study.⁴ HLA-B*57:01 and HLA-A*31:01 alleles were present in 55.26% (21/38) of patients with CBZ-SCAR

($P = 3.58 \times 10^{-11}$). Thus, our findings suggest that the combination of HLA-B*57:01 and HLA-A*31:01 screening as a preemptive test may be able to reduce CBZ-SCAR in Europeans.

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CONFLICT OF INTEREST

The authors have declared that they have no conflict of interest.

FUNDING INFORMATION

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patients with Stevens-Johnson syndrome. *J Allergy Clin Immunol.* 2012;129(6):1562-1569.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Obesity causes pulmonary dysbiosis affecting innate immune response in murine asthma model

To the Editor,

The recent efforts towards the comprehension of asthma pathogenesis have been strongly associated with reduction of exposure to microorganisms, frequent antibiotic treatment, birth delivery mode, diet and obesity.¹ In fact, high-fat diet (HFD) and obesity are known to affect pulmonary immunity and hyperresponsiveness; it also causes gut dysbiosis contributing to the observed changes in the lungs.² In addition, clinical and experimental studies have demonstrated different immune phenotype in obese asthmatic subjects, characterized by neutrophilia and higher IL-17A levels in the lungs.^{3,4} In the present study, HFD efficiently induced obesity in female Balb/c mice (Figure S1B). After ovalbumin (OVA) sensitizations and challenges (Figure S1A), obese mice displayed reduced IL-4 (Figure S1C) and increased IL-17A levels (Figure S1D) in lung homogenates, associated with diminished eosinophil counts (Figure S1E) and increased MPO⁺ cell, indicating neutrophil presence (Figure S1F), compared to lean-allergic mice, at 48 hours, in accordance with Silva et al.⁴ Importantly, obese mice presented higher IL-17A levels (Figure S1D) when compared to control group, suggesting a homeostasis disruption, regardless of the allergy induction.⁵ In addition, goblet cells, hyperplasia and mucus production, were more intense in the OB/PA group compared to those of the PA group at both studied time-points (Figure S1I).

Regarding the peculiar phenotype observed in the lungs of OB/PA group, we investigated the activation of DCs by flow cytometry (Figure S3), through the evaluation of the expression of the activation marker, CD80; the receptors of innate immune, Toll-like receptor 2/4; and the inhibitory ligand, PDL-1 (Figure 1A-D). In OB group, expression of TLR-2 (Figure 1A) and CD80 (Figure 1C) was smaller than in CN group, while the expression of TLR-4 (Figure 1B) and

PDL-1 (Figure 1D) was increased. Moreover, obese mice subjected to pulmonary allergy protocol showed reduction of TLR-2 (Figure 1A), TLR-4 (Figure 1B), CD80 (Figure 1C) and PDL-1 (Figure 1D) in comparison with the nonobese allergic group (PA), at the 24-hour time-point. Nevertheless, 48 hours after the last challenge all of these markers presented a greater expression than in 24 hours, in the OB/PA group, while this effect was not noticed in the PA group.

It is known that obesity can be caused by dysbiosis of intestinal microbiota and that diet can affect mainly Firmicutes and Bacteroidetes.⁶ Along these lines, qPCR showed an increased percentage of Firmicutes and reduction of Bacteroidetes in OB group, in comparison with CN group (Figure S2B), and augment of Firmicutes/Bacteroidetes ratio in the gut of OB group, in comparison with CN group (Figure S2A-B). Furthermore, pulmonary allergy induction increased Firmicutes/Bacteroidetes ratio in PA and OB/PA groups, when compared to CN group (Figure S2A-B).

Recent evidence indicates that lungs are not sterile.^{7,8} In the work, all the main phyla were detected through fluorescent in situ hybridization (FISH),⁹ and specific probes (Data S1) allowed the counting of Bacteroidetes (Figure S5A), Fusobacteria (Figure S5B), Firmicutes (Figure 1E), Proteobacteria (Figure 1F) and Actinobacteria (Figure 1G), in the lungs. Interestingly, obesity reduced the number of Firmicutes (Figure 1E) and increased Proteobacteria (Figure 1F), when compared to nonallergic lean mice. After the induction of allergy, the number of Bacteroidetes (Figure S5A) and Firmicutes (Figure 1E) was significantly higher, in the allergic groups (PA) and (OB/PA) in comparison with the nonallergic mice (CN and OB). In addition, the Proteobacteria phylum (Figure 1B) was more abundant in nonobese allergic (PA) animals, but it did not show any significant growth in obese allergic (OB/PA) mice. Regardless of the reduction in the Proteobacteria phylum, the qPCR relative quantification has shown the *Moraxella catarrhalis*/Proteobacteria proportion to be increased in obese asthmatic (Figure 1D). This bacterial persistence possibly contributed to the immune profile shift, as this species is

Abbreviations: BMDC, bone marrow-derived dendritic cell; CN, control negative; DC, dendritic cell; EUB, Eubacteria; FISH, fluorescent in situ hybridization; HFD, high-fat diet; IL, interleukin; MPO, myeloperoxidase; OB, obese; OB/PA, obese/pulmonary allergy; OVA, ovalbumin; PA, pulmonary allergy; PDL-1, programmed death ligand - 1; qPCR, quantitative polymerase chain reaction; Th2, T helper 2; TLR, Toll-like receptor.

Supporting information

Methods

HLA genotyping

HLA-A and *HLA-B* genotypes of 31 patients with CBZ-SJS/TEN were determined by SeCore HLA sequence-based typing (Invitrogen, Life Technologies, Carlsbad, CA). The *HLA* genotypes of patients with CBZ-DRESS and European general population controls were performed as described previously(1, 2). The European general population controls were mainly enrolled from Central Europe(2). We compared the allele frequencies of HLA data from our European general population controls with those of European population controls of the 1000 Genomes Project (1000G EUR; data obtained from Abi-Rached L et al.(3)). The results show that most of the HLA allele frequencies are similar (**Table S5**). We further evaluated the HLA associations of CBZ-SJS/TEN by using our European general population controls and controls of 1000G EUR, respectively. It revealed similar results of HLA association by using different general population databases (**Table S2** and **Table S3**).

Surface plasmon resonance measurement and analysis

The recombinant proteins HLA-B, endogenous peptide, and β 2-microglobulin were purified from the C1R transfectants by using an affinity column coated with w6/32 antibody, as previously described(4). The Biacore T200 surface plasmon resonance (SPR) biosensor (GE Healthcare, Piscataway, NJ) was used for analyzing the interaction between HLA-B proteins and CBZ. Briefly, we immobilized the recombinant HLA-B proteins (acting as ligands) on the chips by means of an amine-coupling reaction, and the immobilized levels of HLA-B protein were 5248-6262 response units. The drugs dissolved in PBS with 5% dimethyl sulfoxide were used for analysis and flowed through the solid phase. Responses of the interaction were reference

subtracted and corrected with a standard curve for the dimethyl sulfoxide effects. The BIA Evaluation software Version 1.0 was used for data analysis.

Statistical analysis

Statistical analyses were performed using SPSS for Windows version 21.0 (IBM, Armonk, NY).

We conducted the statistical analysis for the association by comparing the allele frequencies between cases and controls in models of inheritance (additive model and dominant model).

Comparisons of genotype frequencies between groups were performed using Fisher exact tests.

To achieve sufficient power to identify HLA loci association, the corrected P (P_c) values were adjusted by using Bonferroni correction for multiple comparisons. P_c value was based on the

raw P value estimated by the number of $\geq 1\%$ HLA alleles present within the loci examined (13

for HLA-A and 20 for HLA-B; based on our general population controls). Odds ratios (ORs)

were calculated according to Haldane modification. Confidence intervals (CIs) and P values for

rate ratio estimates were calculated using a 2-sided test. Differences were considered statistically significant at P -values of less than 0.05.

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Supplementary tables

Table S1. *HLA-A* and *HLA-B* genotypes of patients with CBZ-induced SJS/TEN in Europeans.

Case No.	Phenotype	Country	HLA-A allele 1	HLA-A allele 2	HLA-B allele 1	HLA-B allele 2
European descent						
1	SJS/TEN overlap	Germany	A*01:01	A*02:01	B*35:02	B*44:02
2	TEN	France	A*02:01	A*02:05	B*50:01	B*51:01
3	SJS	Germany	A*01:01	A*24:02	B*08:01	B*27:07
4	SJS	Israel	A*24:02	A*29:01	B*18:01	B*73:01
5	SJS/TEN overlap	Italy	A*26:01	A*36:01	B*38:01	B*57:01
6	SJS/TEN overlap	Hungary	A*26:01	A*26:01	B*38:01	B*38:01
7	SJS/TEN overlap	France	A*02:01	A*26:01	B*13:02	B*57:01
8	SJS	Poland	A*01:01	A*33:01	B*45:01	B*57:01
9	SJS/TEN overlap	Germany	A*01:01	A*31:01	B*08:01	B*51:01
10	SJS	Germany	A*26:01	A*30:01	B*08:01	B*38:01
11	SJS	Albany	A*02:01	A*68:01	B*18:01	B*51:01
12	SJS	Germany	A*01:01	A*31:01	B*08:01	B*39:01
13	SJS	Germany	A*01:01	A*66:01	B*07:02	B*41:02
14	SJS	Germany	A*02:01	A*23:01	B*41:01	B*49:01
15	SJS/TEN overlap	Germany	A*02:01	A*25:01	B*08:01	B*40:01
16	SJS	Germany	A*01:01	A*29:02	B*44:03	B*57:01
17	SJS	Germany	A*01:01	A*02:01	B*44:03	B*57:01
18	SJS	Germany	A*25:01	A*31:01	B*13:02	B*18:01
19	SJS/TEN overlap	Germany	A*02:01	A*23:01	B*44:03	B*44:03
20	SJS	Germany	A*01:01	A*66:01	B*08:01	B*41:02
21	TEN	Germany	A*01:01	A*01:01	B*08:01	B*57:01
22	SJS	Germany	A*24:02	A*26:01	B*35:01	B*38:01
23	SJS/TEN overlap	France	A*01:01	A*03:01	B*08:01	B*35:03
24	SJS	Germany	A*01:01	A*30:02	B*08:01	B*57:01
25	SJS/TEN overlap	Germany	A*01:01	A*02:01	B*13:02	B*57:01
26	SJS/TEN overlap	Germany	A*02:01	A*03:01	B*07:02	B*57:01
27	SJS	France	A*01:01	A*31:01	B*57:01	B*57:01
28	SJS	Germany	A*02:01	A*29:02	B*44:03	B*57:01
Vietnamese						
29	TEN	France	A*02:01	A*11:01	B*15:02	B*44:02
30	TEN	France	A*02:01	A*11:01	B*15:02	B*44:02
Thai people						
31	SJS	Germany	A*02:07	A*34:01	B*15:21	B*46:01

Table S2. Association of *HLA-A* and *HLA-B* alleles with CBZ-induced SJS/TEN compared with the European general population controls.

HLA Genotype	SJS/TEN N (%)	European General population* N (%)	OR (95% CI)	P values	Pc values
HLA-A					
A*01:01	14/28 (50.0%)	2731/8862 (30.82%)	2.2 (1.1-4.7)	0.039	0.503
A*02:01	11/28 (39.29%)	5118/8862 (57.75%)	0.5 (0.2-1.0)	0.056	0.724
A*24:02	3/28 (10.71%)	1572/8862 (17.74%)	0.6 (0.2-1.8)	0.460	-
A*26:01	5/28 (17.86%)	530/8862 (5.99%)	3.5 (1.3-9.0)	0.024	0.313
A*31:01	4/28 (14.29%)	396/8862 (4.52%)	3.5 (1.2-10.2)	0.035	0.455
HLA-B					
B*08:01	8/28 (28.57%)	1835/8862 (20.71%)	1.5 (0.7-3.5)	0.348	-
B*13:02	3/28 (10.71%)	549/8862 (6.2%)	1.8 (0.5-6.0)	0.251	-
B*15:02	0/28 (0%)	3/8862 (0.034%)	44.4 (2.2-879.5)	1	-
B*18:01	3/28 (10.71%)	838/8862 (9.46%)	1.1 (0.3-3.8)	0.744	-
B*38:01	4/28 (14.29%)	330/8862 (3.72%)	4.3 (1.5-12.5)	0.020	0.392
B*44:02	1/28 (3.57%)	1428/8862 (16.11%)	0.2 (0.0-1.4)	0.074	-
B*44:03	4/28 (14.29%)	726/8862 (8.19%)	1.9 (0.6-5.4)	0.284	-
B*57:01	11/28 (39.29%)	593/8862 (6.69%)	9.0 (4.2-19.4)	9.62 x 10⁻⁷	1.83 x 10⁻⁵

Only patients with European descent (N=28) were included for HLA analysis. Two Vietnamese patients from France and one Thai patient from Germany were not included for analysis. *The control HLA results were adapted from our published data of the general population controls from Central Europe(2).

Table S3. Association of *HLA-A* and *HLA-B* alleles with CBZ-induced SJS/TEN compared with the European general population controls of 1000 Genomes Project (1000G EUR).

HLA Genotype	SJS/TEN N (%)	1000G EUR General population[#] N (%)	OR (95% CI)	P values	Pc values
HLA-A					
A*01:01	14/28 (50.0%)	124/529 (23.44%)	3.3 (1.5-7.0)	0.003	0.060
A*02:01	11/28 (39.29%)	274/529 (51.80%)	0.6 (0.3-1.3)	0.245	-
A*24:02	3/28 (10.71%)	90/529 (17.01%)	0.6 (0.2-2.0)	0.602	-
A*26:01	5/28 (17.86%)	30/529 (5.67%)	3.6 (1.3-10.2)	0.025	0.500
A*31:01	4/28 (14.29%)	26/529 (4.91%)	3.2 (1.0-10.0)	0.056	1.131
HLA-B					
B*08:01	8/28 (28.57%)	85/529 (16.07%)	2.1 (0.9-4.9)	0.113	-
B*13:02	3/28 (10.71%)	29/529 (5.48%)	2.1 (0.6-7.3)	0.213	-
B*15:02	0/28 (0%)	0/529 (0%)	18.6 (0.4-953.5)	1	-
B*18:01	3/28 (10.71%)	41/529 (7.75%)	1.4 (0.4-4.9)	0.478	-
B*38:01	4/28 (14.29%)	20/529 (3.78%)	4.2 (1.3-13.4)	0.027	0.541
B*44:02	1/28 (3.57%)	87/529 (16.45%)	0.2 (0.0-1.4)	0.105	-
B*44:03	4/28 (14.29%)	62/529 (11.72%)	1.3 (0.4-3.7)	0.762	-
B*57:01	11/28 (39.29%)	45/529 (8.51%)	7.0 (3.1-15.8)	2.29 x 10⁻⁵	4.58 x 10⁻⁴

Only patients with European descent (N=28) with CBZ-SJS/TEN were included for HLA analysis.

[#]The control HLA results were obtained from 1000 Genomes Project (EUR) as described previously(3).

Table S4. *HLA-A* and *HLA-B* genotypes of patients with CBZ-induced DRESS in European descent patients.

Case No.	Phenotype	Country	HLA-A allele 1	HLA-A allele 2	HLA-B allele 1	HLA-B allele 2
European descent						
E1	DRESS	France	26	31:01	35	40
E2	DRESS	France	32	74	14	14
E3	DRESS	Germany	11	31:01	08	40
E4	DRESS	France	31:01	34	08	56
E5	DRESS	France	30	31:01	18	40
E6	DRESS	Germany	02	31:01	07	13
E7	DRESS	Germany	11	31:01	35	39
E8	DRESS	France	02	02	14	44
E9	DRESS	Germany	30	31:01	13	51
E10	DRESS	France	68	74	35	42

The *HLA-A* and *HLA-B* alleles were determined by polymerase chain reaction using sequence specific primers (PCR-SSP, Genovision kit). The presence of *HLA-A*31:01* alleles in samples was further analyzed by commercially available *HLA-A*31* high resolution typing kits (Olerup-SA; 141 Bionobis, France).

Table S5. Comparison of HLA allele frequencies between two datasets of European population controls.

HLA Genotype	1000G EUR General population[#] N (%)	European General population* N (%)
HLA-A		
A*01:01	124/529 (23.44%)	2731/8862 (30.82%)
A*02:01	274/529 (51.80%)	5118/8862 (57.75%)
A*24:02	90/529 (17.01%)	1572/8862 (17.74%)
A*26:01	30/529 (5.67%)	530/8862 (5.99%)
A*31:01	26/529 (4.91%)	396/8862 (4.52%)
HLA-B		
B*08:01	85/529 (16.07%)	1835/8862 (20.71%)
B*13:02	29/529 (5.48%)	549/8862 (6.2%)
B*15:02	0/529 (0%)	3/8862 (0.03%)
B*18:01	41/529 (7.75%)	838/8862 (9.46%)
B*38:01	20/529 (3.78%)	330/8862 (3.72%)
B*44:02	87/529 (16.45%)	1428/8862 (16.11%)
B*44:03	62/529 (11.72%)	726/8862 (8.19%)
B*57:01	45/529 (8.51%)	593/8862 (6.69%)

[#]The HLA results were obtained from 1000 Genomes Project (EUR) as described previously(3)

*These HLA results of European general population controls were obtained from Central Europe from our published data(2).