Pharmacological Research 115 (2017) 168–178

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Significant HLA class I type associations with aromatic antiepileptic drug (AED)-induced SJS/TEN are different from those found for the same AED-induced DRESS in the Spanish population

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ARTICLE INFO

Article history:
Received 20 June 2016
Received in revised form
21 November 2016
Accepted 21 November 2016
Available online 22 November 2016

Chemical compounds studied in this article:
Phenytoin (PubChem CID: 1775)
Lamotrigine (PubChem CID: 3878)
Carbamazepine (PubChem CID: 2554)
Phenobarbital (PubChem CID: 4763)

Keywords:
Severe cutaneous adverse drug reactions
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Drug reaction with eosinophilia and systemic symptoms
Aromatic antiepileptic drugs
Human leukocyte antigen

ABSTRACT

Aromatic antiepileptic drugs (AEDs) are among the drugs most frequently involved in severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reactions with eosinophilia and systemic symptoms (DRESS). This study investigated the associations between the genetic polymorphisms of HLA class-I and AED-induced SCARs in the Spanish population. HLA class-I genotypes were determined in AED (phenytoin[PHT],lamotrigine[LTG],carbamazepine[CBZ],phenobarbital[PB])-induced SJS/TEN (n = 15) or DRESS (n = 12) cases included in the Spanish SCAR registry, PIEL*enRed*. There were 3 control groups: (A)tolerant to a single AED, (B)tolerant to any AED, and (C)Spanish population controls. For SJS/TEN, concomitant HLA-A*02:01/Cw15:02 alleles were significantly associated with PHT-cases compared to control groups B and C [(B)odds ratio(OR):14.75, p = 0.009;(C)OR:27.50, p < 0.001], and were close to significance with respect to control group A (p = 0.060). The genotype frequency of the HLA-B*38:01 was significantly associated with PHT-LTG-cases compared with the 3 groups of controls [(A)OR:12.86, p = 0.012;(B)OR:13.81; p = 0.002;(C)OR:14.35, p < 0.001], and with LTG-cases [(A)OR:147.00, p = 0.001;(B)OR:115.00, p < 0.001;(C)OR:124.70, p < 0.001]. We found the HLA-B*15:02 allele in a Spanish Romani patient with a CBZ-case. The HLA-A*11:01 was significantly associated with CBZ-cases [(A)OR:63.89, p = 0.002;(B)OR:36.33, p = 0.005;(C)OR:28.29, p = 0.007]. For DRESS, the HLA-A*24:02 genotype frequency was statistically significant in the PHT-LTG-cases [(A)OR:22.56, p = 0.003;(B)OR:23.50. p = 0.001; (C)OR:33.25, p < 0.001], and in the LTG-cases [(A),OR:49.00, p = 0.015;(B)OR:27.77, p = 0.005; (C)OR:34.53, p = 0.002]. HLA-A*31:01 was significantly associated with the CBZ-cases [(A)OR:22.00, p = 0.047;(B)OR:29.50, p = 0.033;(C)OR:35.14, p = 0.006]. In conclusion, we identified several significant genetic risk factors for the first time in the Spanish Caucasian population: HLA-A*02:01/Cw*15:02 combination as a risk factor for PHT-induced SJS/TEN, HLA-B*38:01

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http://dx.doi.org/10.1016/j.phrs.2016.11.027

for LTG- and PHT- induced SJS/TEN, HLA-A*11:01 for CBZ-induced SJS/TEN, and HLA-A*24:02 for LTG- and PHT- induced DRESS. The strong association between HLA*31:01 and CBZ-DRESS in Europeans was confirmed in this study.

1. Introduction

Severe cutaneous adverse drug reactions (SCARs) have distinct clinicopathological features. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are mucocutaneous blistering reactions that result in extensive detachment of the skin and mucous membranes, with high mortality rates ranging from 10% to 50% [1]. SJS and TEN differ only with respect to the amount of skin detachment relative to the body surface area involved [2]. Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS), is characterised by generalised maculopapular eruption (MPE) or erythroderma, high fever, lymphadenopathy, eosinophilia, atypical lymphocytes, and visceral involvement, with a mortality rate of about 10% [3]. Severe mucosal involvement has been more frequently observed in SJS/TEN. The liver is the most frequently involved organ in DRESS. DRESS and SJS/TEN are T-cell-mediated, delayed (type IV) hypersensitivity reactions [4]. The skin symptoms in type IV hypersensitivity are triggered by activation of the specific T cells CD4+ and CD8+, and have been further subclassified in 4 categories. Type IVc reactions (SJS/TEN), are predominantly mediated by cytotoxic T cells (CTLs) and natural killer cells [5–7]. Type IVb reactions (DRESS) are mediated by dysregulated CTLs, helper T cells, and regulatory T cells [8–10]. Delayed hypersensitivity reactions are often an overlap of cytokine and cellular immune responses, with one preferential pathway dominating the final clinical picture.

Although more than 100 drugs have been associated with the development of SJS/TEN or DRESS, aromatic antiepileptic drugs (AEDs) such as phenytoin (PHT), carbamazepine (CBZ), lamotrigine (LTG), and phenobarbital (PB) are among the drugs most frequently involved. AEDs can induce potentially life-threatening hypersensitivity reactions such as SJS/TEN at a frequency of 1 in 10,000 to 1 in 1000 treated patients [11]. For DRESS, it ranges from 1 to 9 per 10,000 patients exposed to the AEDs, CBZ and PHT [12], and appears to be higher among patients taking LTG (1 per 300 adults and 1 per 100 children exposed) [13]; although severe rashes are rare when using the currently recommended titration rate [14].

An increasing number of associations between SCARs and alleles of the human leukocyte antigen (HLA) genes have been identified. They are drug specific and vary among ethnic groups [15–18].

We conducted a study in Spain to examine the association of HLA class I alleles with SJS/TEN or DRESS induced by AEDs in the Spanish population. Secondary aims were to assess the clinical usefulness of HLA as a predictor of AED-induced SJS/TEN or DRESS.

2. Materials and methods

2.1. Patients and controls

Cases of SJS/TEN or DRESS due to AEDs (phenytoin [PHT], lamotrigine [LTG], carbamazepine [CBZ], phenobarbital [PB]) included in the PIEL*enRed* registry of SCARs from medications were included. Controls tolerant to various aromatic AEDs for at least 3 months without any sign of adverse drug reactions (ADRs) were also included in the PIEL*enRed* study. HLA class I alleles from Spanish patients and families awaiting unrelated haematopoietic stem cell donors from the same geographical area, with the selection criterion that haplotypes could be assigned with certainty to both the patient and at least one parent, were used as population controls [19]. In the study, we used 3 different groups of controls: (A) tolerant to a single AED, (B) tolerant to any AED, and (C) Spanish patients awaiting unrelated haematopoietic stem cell transplants as population controls. All the patients provided informed consent for studies involving epidemiology, cellular mechanisms, and genetics. Approval was obtained from the Institutional Review Board at Principe de Asturias University Hospital. The sample size was calculated to detect a specified odds ratio (OR) >5, with a given power of 80% and a type I error of 0.05.

2.2. Diagnosis validation of potential cases

Potential DRESS was diagnosed as possible, probable, or definitive (a score of 2 or more) when the case was evaluated, using the scoring system proposed by Kardaun et al. [20].

The DRESS or SJS/TEN cases included in PIEL*enRed* were also included in the RegiSCAR study group and were validated by an expert committee from either PIEL*enRed* or RegiSCAR.

2.3. Assessment of drug causality

Drug causality assessment for DRESS was performed using the algorithm of the Spanish Pharmacovigilance System [21]. This algorithm evaluates the following parameters: the chronology, which is the interval between drug administration and effect; the literature defining the degree of knowledge of the relationship between the drug and effect; the evaluation of drug withdrawal; the rechallenge effect; and the alternative causes. The final evaluation is listed as follows: <0, improbable (not related); 1–3, conditional (not related); 4–5, possible (related); 6–7, probable (related); or ≥8, definitive (related) cases. The causality assessment for SJS/TEN was performed using the ALDEN algorithm [22]. This algorithm evaluates the delay from initial drug component intake to the onset of the reaction (index day), if the drug is present in the body on the index day, prechallenge/rechallenge, dechallenge, the available information about the relationship with the reaction with this type of drug (notoriety), and the existence or not of alternative causes. The final evaluation is listed as <0, very unlikely (not related); 0–1, unlikely (not related); 2–3 possible (related); 4–5 probable (related); or ≥6 very probable (related) cases.

2.4. LTT assay

A lymphocyte transformation test (LTT) was performed following standard procedures in order to confirm the culprit drug [23]. Briefly, triplicate cultures were established for 6 days in standard culture medium plus 5% autologous serum, in the presence or absence of each drug. ^{3}H-thymidine (0.5 μCi/well) was added to the cultures 18 h before harvesting. Proliferation was estimated as ^{3}H-thymidine uptake measured in counts per minute (cpm) incorporated into DNA. A stimulation index (SI) was calculated as the ratio of mean cpm values between drug-stimulated and unstimulated cell cultures. The test was considered positive when SI was ≥2.

2.5. HLA typing

The polymerase chain reaction–sequence-specific oligonucleotide method combined with Luminex technology was performed using LABType SSO HLA class I commercial kits (One Lambda, Inc., Canoga Park, CA, USA), which provide high resolution (4-digit) typing, following the manufacturer's protocol. The samples were read by means of the flow cytometry platform LABScan 100 (One Lambda, Inc.), followed by an analysis by HLA Fusion software version 3.4 (One Lambda, Inc.). The Immunology laboratory of Ramón y Cajal University Hospital is certified and accredited by the appropriate International Standards Organisation (ISO 9001:2000 and ISO 15189).

2.6. Data analysis

HLA allele frequency was calculated. Fisher's exact test was used to assess the differences between individuals carrying the HLA allele among the cases (by drug per entity, by drug, and by entity) and controls (by drug, by AED, by population). Odds ratio (OR) and 95% confidence interval (CI) values were obtained, and a p-value < 0.05 (two-tailed) was considered statistically significant. In cases with zero in cells, the OR was determined using Haldane's modification, which adds 0.5 to cells if zero. The positive predictive value (PPV), the negative predictive value (NPV), the number needed to diagnose (NND), and the number needed to misdiagnose (NNM) were calculated in the most meaningful comparisons. The statistical analyses were conducted using SPSS software version 20.0 (IBM Corporation, USA).

3. Results

Twenty-seven cases of SJS/TEN or DRESS by AEDs (PHT, LTG, CBZ, PB) included in the Spanish PIEL*enRed* registry were analysed. Of these, 15 cases were SJS/TEN (9 cases by PHT, 3 cases by LTG, 2 cases by CBZ, 1 case by PB), 12 cases were DRESS (5 cases by PHT, 3 cases by LTG, 4 cases by CBZ). The case of SJS/TEN by PB was excluded for analysis purposes. Finally, 26 Spanish cases were included in the analysis (median age at exposure 50 years, range 3–91 years; female 61.5%). Characteristics, LTT results, and HLA genotypes of the cases are shown in Table 1. All the patients included a single AED of high causality (probable, very probable), except in one case (n° 501-0136) in which the causality of allopurinol was also considered probable.

Sixty-seven controls tolerant to various aromatic AEDs for at least 3 months without any sign of an ADR were included (median number of AEDs 1.0, range 1–2). Eleven (16%) had been exposed to more than one AED. Three controls, however, were finally excluded due to non-Caucasian ethnicity (one was from Vietnam, one was from Sudan, and there was one African-American). The extracted DNA was insufficient for typing HLA class I in 3 controls and thus were also excluded. Ultimately, 61 Spanish Caucasian controls were included in the analysis (median age at exposure 58 years, age range 12–88 years; 52.5% female).

The HLA genotypes of SJS/TEN cases per drug are shown in Table 2. Concomitant HLA-A*02:01 and HLA-Cw*15:02 alleles (3 carriers of 9 cases, 33.3%) were statistically significant in the PHT-induced SJS/TEN, with respect to the AED tolerant group and with respect to the general population group, and were close to significance with respect to the PHT-tolerant group (p = 0.060). We found one HLA-Cw*15:02 allele in 3 cases of PHT-induced SJS/TEN that was significantly associated with respect to the general population group (p = 0.021), but this association did not appear in the other control groups. The genotype frequency of the HLA-B*38:01 (3 carriers of 3 cases, 100%) allele was significantly higher in the LTG-induced SJS/TEN group and in the PHT-LTG SJS/TEN group (5 carriers of 12 cases, 41.7%) compared with the 3 groups of controls. It is of note that the 3 cases were carriers of this allele, and none of the individuals in the LTG-tolerant group was a carrier of HLA-B*38:01. The PPV of the HLA-B*38:01 allele for LTG-induced SJS/TEN compared with the LTG-tolerant was 100% (95% CI: 38–100), the NPV was 100% (95% CI: 81.4–100), the NND was 1.15 (95% CI: 1.00–5.16), and the NNM was 8.67 (95% CI: 3.49–18.67). One patient with LTG-induced SJS/TEN was a carrier of the HLA-Cw*12:04/05 (1 of 3, 33.3%) allele, compared with neither of these two alleles (Cw*12:04, Cw*12:05) in the 3 control groups. We found one HLA-A*69:01 (1 of 3, 33.3%) allele in 1 case of LTG-induced SJS/TEN, compared with no allele in the population control groups (p < 0.001), but this association did not appear in the other control groups. We found the HLA-B*15:02 (1 carrier of 2 cases, 50%) allele in a Spanish Romani patient with CBZ-induced SJS/TEN; this allele was absent in all 3 control groups. Similarly, the HLA-Cw*08:01 allele was found in the same patient with CBZ-induced SJS/TEN and was absent in the CBZ- or AED-exposed control groups. One allele was detected in the population group (1 carrier of 253 controls, 0.4%). We found HLA-A*11:01 (2 carriers of 2 cases, 100%) to be significantly associated with CBZ-induced SJS/TEN, when compared with the 3 groups of controls.

The HLA genotypes of DRESS cases per drug are shown in Table 3. We found one HLA-Cw*17:01 (1 carrier of 5 cases, 20%) allele in 1 case of PHT-induced DRESS, compared with one in the population control groups (p = 0.038), but this association did not appear in the other control groups. The HLA-A*24:02 frequency was statistically significant in the LTG-induced DRESS (3 carriers of 3 cases, 100%) and in the PHT-LTG-induced DRESS (6 carriers of 8 cases, 75%) with respect to the 3 groups of controls. We found two HLA-B*18:01 alleles in 2 of 3 cases (66.7%) of LTG-induced DRESS compared with no allele in the LTG-tolerant (p = 0.080); 5 (4.1%) alleles in the AED-tolerant control group (p = 0.030); and 46 (9.1%) alleles in the general population (p = 0.182). We found the HLA-B*39:05 allele (1 carrier of 3 cases, 33.3%) in one patient with LTG-induced DRESS; this allele was not found in any of the control groups analysed. The genotype frequency of the HLA-A*31:01 allele (2 carriers of 4 cases, 50%) was significantly higher in the cases of CBZ-induced DRESS compared with the 3 groups of controls. We found one HLA-A*33:03 allele and one HLA-A*66:01 allele (1 of 4 cases, 25%) in 2 cases of CBZ-induced DRESS, which was a significant association when compared with the general population (p = 0.046 and p = 0.034, respectively), but this association only appeared in the AED-tolerant group for HLA-A*33:03. The associations between HLA alleles and the entities are shown in Supplementary Tables 2a (SJS/TEN), and 3a (DRESS). The associations between 4-digit HLA alleles and AED-induced SJS/TEN/DRESS per drug are summarised in Supplementary Tables 4 (PHT), 5 (LTG), and 6 (CBZ).

4. Discussion

This article highlights the differences in the HLA class I alleles associated with two different entities of SCAR by AED, SJS/TEN and DRESS. Significant genetic factors associated with SJS/TEN (HLA-A*02:01/Cw*15:02 combination for PHT, HLA-B*38:01 for LTG-PHT, HLA-A*11:01 for CBZ) were different than genetic risk factors associated with DRESS (HLA-A*24:02 for PHT-LTG cases, and HLA-A*31:01 for CBZ cases). HLAs are an important family of genes involved in the adaptive immune responses. Their primary function is to allow the host immune system to be able to distinguish between self and non-self peptides. However, these genes have also been implicated in some chronic inflammatory diseases and autoimmune diseases. Major histocompatibility complex class I molecules are heterodimers that consist of two polypeptide chains,

Table 1
Characteristics and HLA genotypes of the patients.

Code PIEL*enRed*	Sex	Age at reaction (yrs)	Ethnicity	Entity	Drug causality	LTT	HLA-A	HLA-B	HLA-Cw
501–0052	Male	16	Caucasian (Romani)	SJS/TEN	CBZ	POS	A*02:01/A*11:01	B*07:02/B*15:02	Cw*07:02/Cw*08:01
501–0054	Female	27	Caucasian	SJS/TEN	CBZ	POS	A*02:01/A*11:01	B*44:02/B*27:05	Cw*05:01/Cw*03:03
501–0020	Female	61	Caucasian	DRESS	CBZ	POS	A*26:01/A*32:01	B*35:01/B*35:02	Cw*04:01/Cw*04:01
501–0235	Male	70	Caucasian	DRESS/MPE	CBZ	POS	A*03:01/A*31:01	B*07:02/B*07:02	Cw*07:02/Cw*07:02
501–0164	Female	42	Caucasian	DRESS	CBZ	POS	A*02:01/A*66:01	B*44:02/B*51:01	Cw*05:01/Cw*14:02
501–0180	Female	84	Caucasian	DRESS	CBZ	POS	A*31:01/A*33:03	B*40:01/B*58:01	Cw*03:04/Cw*03:02
501–0001	Female	34	Caucasian	SJS/TEN	LTG	POS	A*26:01/A*69:01	B*44:02/B*38:01	Cw*08:02/Cw*12:04/05
501–0035	Male	3	Caucasian from North Africa	SJS/TEN	LTG	POS	A*01:01/A*11:01	B*49:01/B*38:01	Cw*07:01/Cw*12:03
501–0072	Male	5	Caucasian	SJS/TEN	LTG	POS	A*03:01/A*02:01	B*35:08/B*38:01	Cw*04:01/Cw*12:03
501–0044	Female	16	Caucasian	DRESS/SJS	LTG	POS	A*24:02/A*02:01	B*15:01/B*39:05	Cw*03:03/Cw*07:02
501–0048	Female	91	Caucasian	DRESS/MPE	LTG	NEG	A*01:01/A*24:02	B*08:01/B*18:01	Cw*07:01/Cw*6/12
501–0066	Female	16	Caucasian	DRESS	LTG	POS	A*24:02/A*24:02	B*18:01/B*27:05	Cw*07:01/Cw*15:02
501–0238	Female	60	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*30:02	B*38:01/B*53:01	Cw*12:03/Cw*15:05
501–0237	Female	32	Caucasian from South America	SJS/TEN	PHT	ND	A*32:01/A*66:01	B*14:01/B*14:02	Cw*08:02/Cw*08:02
501–0236	Female	76	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*80:01	B*44:03/B*44:02	Cw*04:01/Cw*04:01
501–0053	Female	25	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*26:01	B*38:01/B*51:01	Cw*12:03/Cw*15:02
501–0056	Male	55	Caucasian	SJS/TEN	PHT	POS	A*02:01/A*25:01	B*18:01/B*07:02	Cw*12:03/Cw*15:02
501–0109	Male	32	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*32:01	B*18:01/B*49:01	Cw*05:01/Cw*07:01
501–0130	Female	68	Caucasian	SJS/TEN	PHT	POS	A*11:01/A*32:01	B*35:01/B*49:01	Cw*04:01/Cw*07:01
501–0135	Male	63	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*02:01	B*08:01/B*15:01	Cw*07:01/Cw*03:03
501–0138	Male	50	Caucasian	SJS/TEN	PHT	ND	A*02:01/A*29:02	B*44:03/B*51:01	Cw*15:02/Cw*16:01
501–0136	Female	58	Caucasian	DRESS	PHT*	NEG	A*23:01/A*24:02	B*49:01/B*50:01	Cw*06:02/Cw*07:01
501–0075	Female	63	Caucasian	DRESS/MPE	PHT	POS	A*02:01/A*03:01	B*14:02/B*44:03	Cw*08:02/Cw*16:01
501–0102	Male	80	Caucasian	DRESS	PHT	ND	A*02:01/A*24:02	B*39:06/B*41:01	Cw*07:02/Cw*17:01
501–0145	Female	41	Caucasian	DRESS	PHT	ND	A*02:01/A*03:01	B*35:03/B*51:01	Cw*03:04/Cw*14:02
501–0186	Male	54	Caucasian	DRESS	PHT	POS	A*24:02/A*68:02	B*53:01/B*15:01	Cw*04:01/Cw*03:03
501–0239	Female	16	Caucasian	SJS/TEN	PB	ND	A*02:01/A*74:01	insufficient DNA sample	Cw*02:02/Cw*04:01

*Probable allopurinol causality was also considered. AED: aromatic antiepileptic drug; CBZ: carbamazepine; DRES: drug reaction with eosinophilia and systemic symptoms; MPE: maculopapular eruption; LTT: lymphocyte transformation test; LTG: lamotrigine; NEG: negative; POS: positive; PHT: phenytoin; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; ND: Not Done.

Table 2
Associations between 4-digit HLA alleles per AED and SJS/TEN.

HLA allele	PHT		AEDs		PHT cases vs. PHT-tolerant		PHT cases vs. ADE-tolerant		PHT cases vs. General Population	
	Cases n = 9	Tolerant n = 28	All tolerant n = 61	Population n = 253	9 cases vs. 28 tolerant		9 cases vs. 61 tolerant		9 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*02:01	7 (77.8)	15 (53.6)	29 (47.5)	133 (52.6)	0.123	6.93 (0.69–168.29)	0.181	3.86 (0.65–29.48)	0.136	3.16 (0.59–22.46)
A*11:01	1 (11.1)	3 (10.7)	7 (11.5)	38 (15.0)	1.000	1.04 (0.04–14.68)	1.000	0.97 (0.04–10.05)	1.000	0.71 (0.03–5.85)
A*25:01	1 (11.1)	0 (0.0)	1 (1.6)	13 (5.1)	0.121	10.06 (0.30–76.02E^6)	0.484	7.50 (0.18–313.05)	0.395	2.331 (0.10–20.96)
A*26:01	1 (11.1)	1 (3.6)	4 (6.6)	4 (1.6)	0.865	3.38 (0.08–1143.42)	1.000	1.78 (0.07–21.70)	0.323	7.78 (0.30–92.76)
A*29:02	1 (11.1)	2 (7.1)	7 (11.5)	49 (19.4)	1.000	1.63 (0.05–28.75)	1.000	0.96 (0.04–10.05)	0.922	0.52 (0.03–4.26)
A*30:02	1 (11.1)	0 (0.0)	1 (1.6)	17 (6.7)	0.121	10.06 (0.30–76.02E^6)	0.484	7.50 (0.18–313.05)	0.957	1.74 (0.08–15.25)
A*32:01	3 (33.3)	2 (7.1)	4 (6.6)	24 (9.5)	0.150	6.50 (0.65–75.71)	0.424	3.00 (0.39–23.69)	0.108	4.77 (0.88–23.54)
A*66:01	1 (11.1)	1 (3.6)	1 (1.6)	1 (0.4)	0.865	3.38 (0.08–1143.42)	0.484	7.50 (0.18–313.05)	0.135	31.50 (0.77–1299.99)
A*80:01	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.121	10.06 (0.30–76.02E^6)	0.083	21.71 (0.65–16.25E^6)	**0.003***	**89.47 (2.72–66.58E^6)**
B*07:02	1 (11.1)	3 (10.7)	12 (19.7)	42 (16.6)	1.000	1.04 (0.04–14.68)	0.937	0.51 (0.02–4.83)	1.000	0.63 (0.03–5.17)
B*08:01	1 (11.1)	2 (3.6)	6 (9.8)	34 (13.4)	1.000	1.63 (0.05–28.75)	1.000	1.15 (0.05–12.39)	1.000	0.81 (0.04–6.70)
B*14.01	1 (11.1)	1 (3.6)	1 (1.6)	9 (3.6)	0.865	3.38 (0.08–1143.42)	1.000	1.15 (0.05–12.39)	0.599	3.39 (0.14–32.69)
B*14.02	1 (11.1)	1 (3.6)	5 (8.2)	18 (7.1)	0.865	3.38 (0.08–1143.42)	1.000	1.40 (0.06–15.90)	0.995	1.63 (0.07–14.25)
B*15:01	1 (11.1)	1 (3.6)	3 (4.9)	13 (5.1)	0.865	3.38 (0.08–1143.42)	0.862	2.42 (0.09–32.96)	0.395	2.331 (0.10–20.96)
B*18:01	2 (22.2)	0 (0.0)	5 (8.2)	46 (18.2)	0.090	19.00 (0.79–13.03E^6)	0.438	3.20 (0.35–25.37)	1.000	1.29 (0.18–7.08)
B*35:01	1 (11.1)	1 (3.6)	5 (8.2)	35 (13.8)	0.865	3.38 (0.08–1143.42)	1.000	1.40 (0.06–15.90)	1.000	0.78 (0.04–6.47)
B*38:01a	2 (22.2)	2 (7.1)	3 (4.9)	13 (5.1)	0.487	3.71 (0.30–48.08)	0.235	5.52 (0.53–53.80)	0.175	6.28 (0.68–32.52)
B*44:02	1 (11.1)	3 (10.7)	4 (6.6)	22 (8.7)	1.000	1.04 (0.04–14.68)	1.000	1.78 (0.06–21.70)	1.000	1.319 (0.06–11.25)
B*44:03	2 (22.2)	2 (7.1)	8 (13.1)	67 (26.5)	0.487	3.71 (0.30–48.08)	0.759	1.89 (0.23–13.17)	1.000	0.79 (0.11–4.31)
B*49:01	2 (22.2)	3 (10.7)	6 (9.8)	13 (5.1)	0.704	2.38 (0.22–24.02)	0.544	2.62 (0.30–19.63)	0.175	6.28 (0.68–32.52)
B*51:01	2 (22.2)	9 (32.1)	18 (29.5)	41 (16.2)	0.908	0.603 (0.07–4.34)	1.000	0.68 (0.09–4.8)	0.902	1.48 (0.20–8-18)
B*53:01	1 (11.1)	0 (0.0)	0 (0.0)	9 (3.6)	0.121	10.06 (0.30–76.02E^6)	0.083	21.71 (0.65 –16.25E^6)	0.599	3.39 (0.14–32.69)
Cw*03:03	1 (11.1)	0 (0.0)	0 (0.0)	14 (5.5)	0.121	10.06 (0.30–76.02E^6)	0.083	21.71 (0.65 –16.25E^6)	0.834	2.13 (0.09–19.19)
Cw*04:01	2 (22.2)	7 (25.0)	13 (21.3)	70 (27.7)	0.925	1.50 (0.22–9.89)	0.756	1.68 (0.29–9.13)	0.961	1.31 (0.25–46.09)
Cw*05:01	1 (11.1)	4 (14.3)	5 (8.2)	45 (17.8)	1.000	0.75 (0.03–9.49)	1.000	1.40 (0.06–15.90)	1.000	0.58 (0.03–4.74)
Cw*07:01	3 (33.3)	6 (21.4)	16 (26.2)	72 (28.5)	0.754	1.83 (0.26–12.60)	0.926	1.40 (0.24–7.52)	1.000	1.26 (0.24–5.86)
Cw*08:02	1 (11.1)	2 (7.1)	4 (6.6)	26 (10.3)	0.487	3.71 (0.30–48.08)	0.353	4.07 (0.42–34.95)	0.496	2.50 (0.34–14.21)
Cw*12:03	3 (33.3)	3 (10.7)	8 (13.1)	34 (13.4)	0.281	4.17 (0.49–37.45)	0.114	3.31 (0.52–20.04)	0.238	3.22 (0.60–15.48)
Cw*15:02	3 (33.3)	3 (10.7)	8 (13.1)	12 (4.7)	0.281	4.17 (0.49–37.45)	0.114	3.31 (0.52–20.04)	**0.021***	**10.04 (1.73–54.19)**
Cw*15:05	1 (11.1)	0 (0.0)	1 (1.6)	7 (2.8)	0.281	10.06 (0.30–76.02E^6)	0.484	7.50 (0.18–313.05)	0.494	4.39 (0.18–44.62)
Cw*16:01	1 (11.1)	3 (10.7)	10 (16.4)	56 (22.1)	1.000	1.04 (0.04–14.68)	0.429	0.64 (0.03–6.20)	0.762	0.44 (0.02–3.57)
Combination										
A*02:01/Cw15:02	3 (16.7)	1 (1.8)	2 (3.3)	5 (1.8)[&]	**0.060**	**13.50 (0.94–409.55)**	**0.009***	**14.75 (1.54–167.00)**	**<0.001***	**27.50 (4.04–187.07)**

Table 2 (*Continued*)

HLA allele	LTG		AEDs		LTG-cases vs. LTG-tolerant		LTG-cases vs. ADEs-tolerant		LTG-cases vs. General Population	
	Cases n = 3	Tolerant n = 10	All tolerant n = 61	Population n = 253	3 cases vs. 10 tolerant		3 cases vs. 61 tolerant		3 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*01:01	1 (33.3)	2 (20.0)	13 (21.3)	50 (19.8)	1.000	2.00 (0.04–78.77)	1.000	1.85 (0.06–29.62)	0.976	2.03 (0.07–29.33)
A*02:01	1 (33.3)	6 (60.0)	29 (47.5)	133 (52.6)	0.874	0.33 (0.01–8.01)	1.000	0.53 (0.02–8.18)	0.929	0.45 (0.02–6.44)
A*03:01	1 (33.3)	3 (30.0)	12 (19.7)	47 (18.6)	1.000	1.17 (0.05–34.03)	1.000	2.04 (0.07–33.05)	0.930	2.19 (0.08–31.72)
A*11:01	1 (33.3)	0 (0.0)	7 (11.5)	38 (15.0)	0.395	10.50 (0.12–11.53E^6)	0.669	3.86 (0.13–68.46)	0.784	2.83 (0.10–41.29)
A*26:01	1 (33.3)	1 (10.0)	4 (6.6)	4 (1.6)	0.846	4.50 (0.08–327.95)	0.439	7.13 (0.21–152.58)	0.115	31.13 (0.91–654.92)
A*69:01	1 (33.3)	0 (0.0)	1 (1.6)	0 (0.0)	0.395	10.50 (0.12–11.53E^6)	0.185	30.00 (0.56–2017.84)	**<0.001***	**304.20(7.18–26.64E^6)**
B*35:08	1 (33.3)	0 (0.0)	0 (0.0)	3 (1.2)	0.395	10.50 (0.12–11.53E^6)	0.091	61.50 (0.77–65.02E^6)	**0.034***	**41.67 (1.15–1032.92)**
B*38:01a	3 (100)	0 (0.0)	3 (4.9)	13 (5.1)	**0.001***	**147.00 (1.88–483)**	**<0.001***	**115.00 (4.68–81.09E^6)**	**<0.001***	**124.70 (6.78–77.76E^6)**
B*44:02	1 (33.3)	1 (10.0)	4 (6.6)	22 (8.7)	0.846	4.50 (0.08–327.95)	0.439	7.13 (0.21–152.58)	0.494	5.25 (0.18–78.61)
B*49:01	1 (33.3)	1 (10.0)	6 (9.8)	13 (5.1)	0.846	4.50 (0.08–327.95)	0.268	4.58 (0.15–84.61)	0.312	9.23 (0.31–144.81)
Cw*04:01	1 (33.3)	2 (20.0)	13 (21.3)	70 (27.7)	1.000	2.00 (0.04–78.77)	1.000	1.85 (0.06–29.62)	1.000	1.31 (0.05–18.75)
Cw*07:01	1 (33.3)	1 (10.0)	16 (26.2)	72 28.52)	0.846	4.50 (0.08–327.95)	1.000	1.41 (0.05–22.12)	1.000	1.26 (0.04–18.02)
Cw*12:03	2 (66.7)	1 (10.0)	8 (13.1)	34 (13.4)	0.217	18.00 (0.47–3602.53)	0.217	18.00 (0.47–3602.24)	0.105	12.88 (0.88–369.75)
Cw*12:04/05	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.395	10.50 (0.12–11.53E^6)	0.091	61.50 (0.77–65.02E^6)	**0.023***	**253.50 (3.24–26.63E^6)**

HLA alleles	PHT-LTG		AEDs		PHT-LTG cases vs.PHT-LTG-tolerant		PHT-LTG cases vs. AED-tolerant		PHT-LTG cases vs. General Population	
	Cases n = 12	Tolerant n = 38	All tolerant n = 61	Population n = 253	12 cases vs. 38 tolerant		12 cases vs. 61 tolerant		12 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
B*38:01 a#	5 (41.7)	2 (5.3)	3 (4.9)	13 (5.1)	**0.012***	**12.86 (1.66–123.82)**	**0.002***	**13.81 (2.18–98.04)**	**<0.001***	**14.35 (3.34–61.53)**

HLA allele	CBZ		AEDs		CBZ cases vs. CBZ-tolerant		CBZ cases vs. ADEs-tolerant		CBZ cases vs. General Population	
	Cases n = 2	Tolerant n = 23	All tolerant n = 61	Population n = 253	2 cases vs 23 tolerant		2 cases vs 61 tolerant		2 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*02:01	2 (100)	8 (34.8)	29 (47.5)	133 (52.6)	0.113	9.12 (0.37–62.61E^6)	0.274	4.84 (0.23–31.46E^6)	0.294	4.51 (0.23–286.11)
A*11:01	2 (100)	4 (17.4)	7 (11.5)	38 (15.0)	**0.002***	**63.89 (2.46–45.61E^6)**	**0.005***	**36.33 (1.54–24.72E^6)**	**0.007***	**28.29 (1.42–180.77)**
B*07:02	1 (50.0)	7 (30.4)	12 (19.7)	42 (16.6)	1.000	2.83 (0.06–128.13)	0.694	4.55 (0.11–183.92)	0.619	5.02 (0.13–188.12)
B*15:02	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	**0.017***	**47.00 (1.08–50.33E^6)**	**0.003***	**123.00 (2.36–13.00E^6)**	**<0.001***	**507.00 (9.88–53.68E^6)**
B*27:05	1 (50.0)	1 (4.3)	3 (4.9)	11 (4.3)	0.303	22.00 (0.30–543.73)	0.248	19.33 (0.40–103.59)	0.184	22.00 (0.56–887.79)
B*44:02	1 (50.0)	0 (0.0)	4 (6.6)	22 (8.7)	**0.017***	**47.00 (1.08–50.33E^6)**	0.307	14.25 (0.31–681.75)	0.345	10.50 (0.28–301.04)
Cw*03:03	1 (50.0)	0 (0.0)	0 (0.0)	14 (5.5)	**0.017***	**47.00 (1.08–50.33E^6)**	**0.003***	**123.00 (2.36–13.00E^6)**	0.229	17.07 (0.44–668.64)
Cw*05:01	1 (50.0)	1 (4.3)	5 (8.2)	45 (17.8)	0.303	22.00 (0.30–543.73)	0.366	11.20 (0.26–506.56)	0.658	4.62 (0.12–172.84)
Cw*07:02	1 (50.0)	6 (26.1)	15 (24.6)	49 (19.4)	0.980	2.83 (0.06–128.11)	0.893	3.07 (0.08–121.38)	1.000	2.12 (0.06–79.58)
Cw*08:01	1 (50.0)	0 (0.0)	0 (0.0)	1 (0.4)	**0.017***	**47.00 (1.08–50.33E^6)**	**0.003***	**123.00 (2.36–13.00E^6)**	**0.031***	**252.00 (3.62–6025.57)**

Bold values are the most significant risk allele or combination for specific AED-induced SJS/TEN.
AED: aromatic antiepileptic drug; CBZ: carbamazepine; E: scientific notation of " x 10"; LTG: lamotrigine; PHT: phenytoin.
*p-value < 0.05 and calculated over a general population of 275 [Balas A et al. 2011). # HLA-B*38:01 from PHT & LTG cases.
a Previously reported to be associated with LTG-induced SJS/TEN

Table 3
Associations between 4-digit HLA alleles per AED and DRESS.

HLA allele	PHT				PHT cases vs. PHT-tolerant		PHT cases vs. ADEs-tolerant		PHT cases vs. General Population	
	Cases n = 5	Tolerant n = 28	All Tolerant n = 61	Population n = 253	5 cases vs. 28 tolerant		5 cases vs. 61 tolerant		5 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*02:01	3 (60.0)	15 (53.6)	29 (47.5)	133 (52.6)	1.000	0.80 (0.08–8.82)	0.941	1.65 (0.20–15.46)	1.000	1.35 (0.18–11.79)
A*03:01	2 (40.0)	6 (21.4)	12 (19.7)	47 (18.6)	0.896	1.89 (0.17–20.50)	0.896	1.88 (0.17–20.50)	0.483	2.92 (0.33–22.30)
A*23:01	1 (20.0)	1 (3.6)	3 (4.9)	19 (7.5)	0.661	5.50 (0.12–269.64)	0.552	4.83 (0.16–83.48)	0.668	3.08 (0.13–32.05)
A*24:02 a	3 (60.0)	8 (28.6)	14 (23.0)	44 (17.4)	0.580	2.81 (0.29–31.65)	0.206	5.04 (0.60–49.06)	0.087	7.13 (0.93–63.11)
A*68:02	1 (20.0)	2 (7.1)	5 (8.2)	4 (1.6)	0.919	2.63 (0.07–58.39)	0.292	3.56 (0.12–54.29)	0.188	15.56 (0.54–232-41)
B*14:02	1 (20.0)	1 (3.6)	5 (8.2)	18 (7.1)	0.661	5.50 (0.12–269.64)	0.778	2.80 (0.10–39.19)	0.640	3.26 (0.13–34.16)
B*15:01	1 (20.0)	1 (3.6)	3 (4.9)	13 (5.1)	0.661	5.50 (0.12–269.64)	0.552	4.83 (0.16–83.48)	0.490	4.62(0.18–50.26)
B*35:03	1 (20.0)	0 (0.0)	2 (3.3)	5 (2.0)	0.069	15.67 (0.41–12.58E^6)	0.427	7.38 (0.21–157.81)	0.224	12.40 (0.45–169.87)
B*39:06	1 (20.0)	2 (7.1)	3 (4.9)	2 (0.4)	0.919	2.63 (0.07–58.39)	0.552	4.83 (0.16–83.48)	0.114	31.38 (0.92–660.15)
B*41:01	1 (20.0)	1 (3.6)	1 (1.6)	3 (1.2)	0.661	5.50 (0.12–269.64)	0.294	15.00 (0.33–717.07)	0.151	20.83 (0.68–353.08)
B*44:03	1 (20.0)	2 (7.1)	8 (13.1)	67 (26.5)	0.919	2.63 (0.07–58.39)	1.000	1.66 (0.06–20.22)	1.000	0.69 (0.03–6.76)
B*49:01	1 (20.0)	3 (10.7)	6 (9.8)	13 (5.1)	1.000	1.66 (0.05–30.19)	0.880	2.28 (0.08–30.21)	0.490	4.62 (0.18–50.26)
B*50:01	1 (20.0)	1 (3.6)	3 (4.9)	4 (1.6)	0.661	5.50 (0.12–269.64)	0.427	7.38 (0.21–157.81)	0.188	15.56 (0.54–232.41)
B*51:01	1 (20.0)	9 (32.1)	18 (29.5)	41 (16.2)	0.797	0.39 (0.01–5.02)	1.000	2.29 (0.08–30.21)	1.000	1.29 (0.06–12.76)
B*53:01	1 (20.0)	0 (0.0)	0 (0.0)	9 (3.6)	0.069	15.67 (0.41–12.58E^6)	**0.013***	**41.00 (1.11–32.51E^6)**	0.361	6.78 (0.26–78.72)
Cw*03:03	1 (20.0)	0 (0.0)	0 (0.0)	14 (5.5)	0.069	15.67 (0.41–12.58E^6)	**0.013***	**41.00 (1.11–32.51E^6)**	0.521	4.27 (0.17–46.00)
Cw*03:04	1 (20.0)	2 (7.1)	6 (9.8)	13 (5.1)	0.919	2.63 (0.07–58.39)	0.427	7.38 (0.21–157.81)	0.490	4.62(0.18–50.26)
Cw*04:01	1 (20.0)	7 (25.0)	13 (21.3)	70 (27.7)	1.000	0.57 (0.02–7.71)	1.000	1.66 (0.06–20.22)	1.000	0.65 (0.03–6.36)
Cw*06:02	1 (20.0)	5 (17.9)	8 (13.1)	25 (9.9)	1.000	1.19 (0.04–19.03)	1.000	1.66 (0.06–20.22)	0.829	2.28 (0.09–23.19)
Cw*07:01	1 (20.0)	7 (25.0)	16 (26.2)	72 (28.5)	1.000	0.57 (0.02–7.71)	1.000	0.70 (0.03–7.68)	1.000	0.63 (0.03–6.11)
Cw*07:02	1 (20.0)	6 (21.4)	15 (24.6)	49 (19.4)	1.000	0.57 (0.02–7.71)	0.206	5.04 (0.60–49.06)	1.000	1.04 (0.04–10.22)
Cw*08:02	1 (20.0)	2 (7.1)	4 (6.6)	26 (10.3)	0.919	2.63 (0.07–58.39)	0.669	3.56 (0.12–54.29)	0.854	2.18 (0.09–22.14)
Cw*14:02	1 (20.0)	3 (10.7)	5 (8.2)	7 (2.8)	1.000	1.66 (0.05–30.19)	0.778	2.80 (0.10–39.19)	0.291	8.86 (0.33–109.21)
Cw*16:01	1 (20.0)	4 (14.3)	10 (16.4)	56 (22.1)	1.000	1.66 (0.05–30.19)	1.000	1.28 (0.05–14.87)	1.000	0.88 (0.04–8.60)
Cw*17:01	1 (20.0)	3 (10.7)	4 (6.6)	1 (0.4)	1.000	1.66 (0.05–30.19)	0.669	3.56 (0.12–54.29)	**0.038***	**63.25 (1.41–2989.60)**

Table 3 (*Continued*)

HLA allele	LTG				LTG cases vs. LTZ-tolerant		LTG cases vs. ADEs-tolerant		LTG cases vs. General Population	
	Cases n = 3	Tolerant n = 10	All Tolerant n = 61	Population n = 253	3 cases vs. 10 tolerant		3 cases vs. 61 tolerant		3 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*01:01	1 (33.3)	2 (20.0)	13 (21.3)	50 (19.8)	1.000	2.00 (0.04–78.77)	1.000	1.84 (0.06–29.62)	1.000	2.03 (0.07–29.33)
A*02:01	1 (33.3)	6 (60.0)	29 (47.5)	133 (52.6)	0.874	0.33 (0.01–8.01)	1.000	0.55 (0.02–8.43)	0.929	0.45 (0.02–6.44)
A*24:02 a	3 (100)	1 (10.0)	14 (23.0)	44 (17.4)	**0.015***	**49.00 (1.25–46.13E^6)**	**0.005***	**27.77 (1.50–17.33E^6)**	**0.002***	**34.53 (2.03–209.71)**
B*08:01	1 (33.3)	0 (0.0)	6 (9.8)	34 (13.4)	0.114	12.60 (0.27–11.53E^6)	0.595	4.58 (0.14–84.61)	0.716	3.22 (0.11–47.14)
B*15:01	1 (33.3)	0 (0.0)	3 (4.9)	13 (5.1)	0.112	12.60 (0.27–11.53E^6)	0.357	9.67 (0.26–243.68)	0.312	9.23 (0.31–44.81)
B*18:01	2 (66.7)	0 (0.0)	5 (8.2)	46 (18.2)	0.080	35.00 (0.81–34.60E^6)	**0.030***	**22.40 (1.23–772.82)**	0.182	9.00 (0.62–256.55)
B*27:05	1 (33.3)	0 (0.0)	3 (4.9)	11 (4.3)	0.112	12.60 (0.27–11.53E^6)	0.357	9.67 (0.26–243.68)	0.269	11.00 (0.36–176.29)
B*39:05	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.112	12.60 (0.27–11.53E^6)	**0.006***	**73.80 (1.72–65.01E^6)**	**<0.001***	**304.20 (7.18–26.63E^7)**
Cw*03:03	1 (33.3)	0 (0.0)	0 (0.0)	14 (5.5)	0.112	12.60 (0.27–11.53E^6)	**0.006***	**73.80 (1.72–65.01E^6)**	0.330	8.54 (0.29–132.80)
Cw*06/12	1 (33.3)	0 (0.0)	–	–	0.112	12.60 (0.27–11.53E^6)	–	–	–	–
Cw*07:01	2 (66.7)	1 (10.0)	17 (27.9)	72 (28.5)	0.217	18.00 (0.47–3603.25)	0.377	5.63 (0.36–169.20)	0.403	5.03 (0.35–142.38)
Cw*07:02	1 (33.3)	3 (30.0)	15 (24.6)	49 (19.4)	1.000	1.17 (0.03–34.03)	1.000	1.53 (0.05–24.25)	0.961	2.08 (0.07–30.09)
Cw*15:02	1 (33.3)	1 (10.0)	8 (13.1)	12 (4.7)	0.217	18.00 (0.47–3603.25)	0.204	2.85 (0.49–258.94)	0.291	10.04 (0.33–159.07)

HLA alleles	Cases n = 8	PHT-LTG Tolerant n = 38	All Tolerant n = 61	Population n = 253	PHT&LTG cases vs. PHT&LTZ-tolerant 8 cases vs. 38 tolerant		PHT&LTG cases vs. ADE-tolerant 8 cases vs. 61 tolerant		PHT&LTG cases vs. General Population 8 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*24:02a #	6 (75.0)	9 (23.7)	15 (24.6)	44 (17.4)	**0.003***	**22.56 (2.19–559.39)**	**0.001***	**23.50 (2.49–553.98)**	**<0.001***	**33.25 (3.95–737.61)**

HLA allele	CBZ				CBZ cases vs. CBZ-tolerant		CBZ cases vs. ADE-tolerant		CBZ cases vs. General Population	
	Cases n = 4	Tolerant n = 23	All Tolerant n = 61	Population n = 253	4 cases vs. 23 tolerant		4 cases vs. 61 tolerant		4 cases vs. 253 controls	
	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	HLA allele positive (%)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
A*02:01	1 (25.0)	8 (34.8)	29 (47.5)	133 (52.6)	1.000	0.63 (0.02–9.16)	0.735	0.37 (0.01–4.37)	0.559	0.30 (0.01–3.29)
A*03:01	1 (25.0)	3 (13.0)	12 (19.7)	47 (18.6)	0.991	2.22 (0.07–46.47)	1.000	1.36 (0.05–17.30)	1.000	1.46 (0.06–16.28)
A*26:01	1 (25.0)	2 (8.7)	4 (3.3)	4 (1.6)	0.789	3.50 (0.09–91.59)	0.560	4.75 (0.15–82.08)	0.152	20.75 (0.68–351.67)
A*31:01 b	2 (50.0)	1 (4.3)	2 (3.3)	7 (2.8)	**0.047***	**22.00 (1.03–1190.36)**	**0.033***	**29.50 (1.73–747.87)**	**0.006***	**35.14 (2.95–434.59)**
A*32:01	1 (25.0)	1 (4.3)	4 (6.6)	24 (9.5)	0.558	7.33 (0.15–397.99)	0.560	4.75 (0.15–82.08)	0.675	3.18 (0.12–36.65)
A*33:03	1 (25.0)	0 (0.0)	0 (0.0)	2 (0.8)	0.111	20.14 (0.50–16.77E^6)	**0.009***	**52.71(1.35–43.34E^6)**	**0.046***	**41.83 (1.15–1037.03)**
A*66:01	1 (25.0)	0 (0.0)	1 (1.6)	1 (0.4)	0.111	20.14 (0.50–16.77E^6)	0.240	20.00 (0.42–1058.44)	**0.031***	**84.00 (1.76–4395.32)**
B*07:02	2 (50.0)	7 (30.4)	12 (19.7)	42 (16.6)	1.000	0.76 (0.03–11.47)	1.000	1.36 (0.05–17.30)	1.000	1.68 (0.07–18.73)
B*35:01	1 (25.0)	4 (17.4)	5 (8.2)	35 (13.8)	1.000	1.58 (0.05–28.72)	0.656	3.73 (0.13–58.71)	0.698	3.04 (0.12–34.93)
B*35:02	1 (25.0)	0 (0.0)	3 (4.9)	7 (2.8)	0.111	20.14 (0.50–16.77E^6)	0.586	6.44 (0.20–129.04)	0.233	12.05 (0.43–166.49)
B*40:01	1 (25.0)	0 (0.0)	2 (3.3)	12 (4.7)	0.111	20.14 (0.50–16.77E^6)	0.352	9.83 (0.27–247.79)	0.377	6.69 (0.25–82.96)
B*44:02	1 (25.0)	0 (0.0)	4 (6.6)	22 (8.7)	0.111	20.14 (0.50–16.77E^6)	0.560	4.75 (0.15–82.08)	0.629	3.50 (0.13–40.59)
B*51:01	1 (25.0)	5 (21.7)	18 (29.5)	41 (16.2)	1.000	1.20 (0.04–19.90)	1.000	0.80 (0.03–9.68)	1.000	1.72 (0.07–19.30)
B*58:01	1 (25.0)	0 (0.0)	2 (3.3)	7 (2.8)	0.111	20.14 (0.50–16.77E^6)	0.352	9.83 (0.27–247.79)	0.115	11.74 (0.42–161.91)
Cw*03:02	1 (25.0)	0 (0.0)	0 (0.0)	4 (1.6)	0.111	20.14 (0.50–16.77E^6)	**0.009***	**52.71(1.35–43.34E^6)**	0.152	20.75 (0.68–351.67)
Cw*03:04	1 (25.0)	3 (13.0)	6 (9.8)	13 (5.1)	0.991	2.22 (0.07–46.47)	0.747	3.06 (0.11–45.12)	0.404	6.15 (0.23–75.39)
Cw*04:01	2 (50.0)	4 (17.4)	14 (23.0)	70 (27.7)	0.409	4.75 (0.33–75.86)	0.503	3.36 (0.30–37.90)	0.626	2.61 (0.26–26.56)
Cw*05:01	1 (25.0)	1 (4.3)	5 (8.2)	45 (17.8)	0.558	7.33 (0.15–397.99)	0.656	3.73(0.13–58.71)	1.000	1.54 (0.06–17.19)
Cw*07:02	2 (50.0)	6 (26.1)	15 (24.6)	49 (19.4)	0.675	2.83 (0.21–39.19)	0.557	2.07 (0.28–34.40)	0.354	4.16 (0.41–42.63)
Cw*14:02	1 (25.0)	1 (4.3)	5 (8.2)	7 (2.8)	0.558	7.33 (0.15–397.99)	0.656	3.73(0.13–58.71)	0.115	11.74 (0.42–161.91)

Bold values are the most significant risk allele for AED-induced DRESS.
AED: aromatic antiepileptic drug; CBZ: carbamazepine; E: scientific notation of " x 10"; LTG: lamotrigine; PHT: phenytoin; MPE: maculopapular eruption.
*p-value < 0.05; # HLA-A*24:02 from PHT & LTG cases.
a Previously reported to be associated with LTG-induced MPE.
b Previously reported to be associated with CBZ-induced DRESS.

α and β2-microglobulin. Only the α chain, also known as a heavy chain, is highly polymorphic, some involving single-nucleotide polymorphisms, and is encoded by an HLA gene. Near the HLA gene, several inflammatory cytokine genes are mapped, such as γ −interferon and tumour necrosis factor-β. If a disease-sensitivity gene exists in close association with a HLA gene, the disease seems to be caused by the HLA type. An association between HLA-B*51 and Behcet's disease is such an example [24]. In the same way, small molecule drugs in close association with HLA genes can cause ADRs. Three models of the interaction of HLA, drug and T cell receptors (TCRs) have been proposed [25]: (1) The "hapten/prohapten" theory. Drugs or their metabolites serve as haptens and bind to the endogenous peptides to form the HLA-peptide-drug complex in the antigen-presenting cells (APCs). This HLA-peptide-drug complex is recognised by TCRs and thus triggers the drug-specific T cell activation. An example of haptenation is covalent binding of benzyl penicilloyl groups, derivative of penicillins, to lysine residues of serum albumin resulting in antibody recognition [26]. (2) The "p-i" (pharmacological interaction with immune receptors) concept. Drugs directly bind to the HLA-peptide complex or TCRs via noncovalent. A peptide is present as part of the HLA-peptide complex, rather that it is not changed by the binding of the drug. In the case of a drug hypersensitivity reaction, the binding of the drug to immune proteins must be sufficient to transmit a stimulatory signal via the TCR [27]. (3) The "altered peptide repertoire" model. Drugs bind to a specific altered peptide repertoire but might not directly bind to pre-existing HLA-peptide complexes. In this sense, modelling and crystallography data have provided evidence that abacavir binds noncovalently to the floor of the peptide-binding groove of HLA-B*57:01, altering the chemistry and shape of the antigen-binding cleft. Such peptides will not have been presented during thymic development of T cells when self-reactive T cells are negatively selected, and thus at least some of these self-peptides have not been previously tolerated and may be recognized by T cells of hypersensitive patients [28]. We have seen that the interaction of a drug with a specific HLA allele can be explained either by a haptenated peptide or noncovalent binding of drug to the HLA or TCR, with or without the involvement of an endogenous peptide. However, these fail to explain why different drug-HLA allele combinations result in such different clinical syndromes. In the present study, we support the hypothesis that the interaction of a drug with the specific HLA allele causing SJS/TEN are different from drug-HLA allele combinations resulting in DRESS.

PHT was the most causative SCAR drug in our cases. Genetic polymorphisms of HLA and cytochrome P450 (CYP) have been explored as key elements for the susceptibility to phenytoin-related SCARs in certain ethnicities. CYPC2 variants, including the CYPC2C9*3 variant, known to reduce the clearance of PHT, have been associated with PHT-induced SCARs in Asian patients [29]. Tassaneeyakul et al. [30] investigated the associations between the genetic polymorphisms of HLA class I and CYP2C9 and PHT-related SCAR in a Thai population. Neither SJS/TEN nor DRESS caused by PHT were significantly associated with the HLA-B*15:02 allele in this population. Six HLA alleles, including HLA-A*33:03, HLA-B*38:02, HLA-B*51:01, HLA-B*56:02, HLA-B*58:01, and HLA-C*14:02 were significantly associated with phenytoin-related SJS/TEN, whereas only HLA-B*51:01 was significantly associated with phenytoin-related DRESS. The CYP2C9*3 variant was significantly associated with PHT-related SJS/TEN, but not with DRESS in this population. To our knowledge, no significant associations of genetic polymorphisms of the HLA- and PHT-induced SJS/TEN or DRESS in European patients have been reported. We have identified a significant association between PHT-induced SJS/TEN and the HLA-A*02:01/Cw*15:02 presence. HLA-C*15:02 in the Spanish population is associated with HLA-B*51:01.[9] Linkage disequilibrium between HLA-A and HLA-C is much lower than that between the HLA-C and HLA-B alleles.

Significant associations between LTG-induced DRESS, PHT-LTG-induced DRESS, and HLA-A*24:02 were detected. A significant association between the HLA-A*24:02 allele and LTG-induced MPE has been described in the Korean population [31] and in Norwegians [32]. This result suggests that the mechanism underlying drug-induced MPE might be similar in DRESS. MPE is the most common allergic reaction affecting the skin, which is observed in approximately 2% to 3% of hospitalised patients [33,34]. Eosinophilia occurs in approximately 50% of most severe maculopapular exanthemas [35]. Eosinophilic drug reactions (EDRs) have recently been described as type IVb reactions [4]. The extent of clinical involvement of EDRs is heterogeneous, ranging from isolated peripheral eosinophilia or single organ involvement (skin, lung, kidney, liver) to systemic disease affecting multiple organs, classically exemplified by DRESS. In patients of European origin, the HLA-B*58:01, HLA-A*68:01, HLA-Cw*07:18, HLA-DQB1*06:09, and HLA-DRB1*13:01 alleles were reported to be weakly associated with LTG-induced SCAR [36], and the HLA-A*02:01:01/B*35:01:01/Cw*04:01:01 haplotype has been suggested as a biomarker for LTG-induced MPE in Mexican Mestizo patients [37]. In our study, no case of HLA-B*58:01, HLA-A*68:01, or HLA-Cw*07:18 was detected. We had just one case (1 carrier of 6 cases, 16.7%) with the HLA-A*02:01/B*35:01/Cw*04:01 haplotype in LTG-induced SCAR, and one haplotype (1 carrier of 3 cases, 33.3%) in LTG-induced SJS/TEN. This haplotype was not found (0 of 10 cases) in the LTG-tolerant group ($p = 0.114$) or in AED-tolerant controls (0 of 61 cases, $p = 0.006$; OR: 73.80; 95% CI: $1.72–65.01*10^6$). The most common haplotype carrying HLA-B*35:01 in the Spanish population includes HLA-A*11:01 and HLA-C*04:01. The HLA-A*02:01:01/B*35:01:01/Cw*04:01:01 haplotype appears in the Spanish population with a frequency of 0.79% (4 carriers of 253 population), which is almost significant compared with the case of SJS induced by LTG ($p = 0.061$; OR: 31.63; 95% CI: 0.92–665.28). We identified significantly strong associations between LTG-induced SJS/TEN and HLA-B*38:01 (compared with LTG-tolerant: PPV = 100%, NPV = 100%, NND = 1.15; NNM = 8.67). Lonjou et al. [38] described a significant association between HLA-B*38:01 and LTG-induced SJS/TEN (4 carriers of 17 cases [24%], 78 of 1822 controls [4.3%], $p = 0.037$; OR: 4.7; 95% CI: 1.3–16) in a RegiSCAR European study, but the authors downplayed the results because the association was weak. Differences in study methodology (their controls were a mixed European population database, as compared with 3 types of controls in ours), could explain the variations in the strength of association.

There is considerable cross-reactivity among various antiepileptic drugs but the mechanisms are not known. CBZ and PHT cause skin rashes in approximately 30% of patients with a history of another AED-related reaction, whereas the risk of LTG causing another cutaneous reaction is somewhat lower, approximately 20% [39]. Interestingly, HLA-B*38:01 carriers were only found in SJS/TEN cases due to LTG or PHT, whereas the HLA-A*24:02 allele was found only in cases of DRESS/MPE due to LTG or PHT. Our results suggest that HLA-B*38:01 is a major responsible allele for the cross-reactivity of SJS/TEN to PHT and LTG. HLA-A*24:02 allele is a major marker for the cross-reactions of DRESS/MPE among PHT and LTG.

The best-known genetic risk factor for an AED-induced SCAR is the association between the HLA-B*15:02 allele and CBZ-induced SJS/TEN, which was first reported in Han Chinese patients [40]. The HLA-B locus is highly polymorphic, and the allele frequency of HLA-B*15:02 varies worldwide. A published meta-analysis summarised studies performed on Chinese, Thai, Malaysian, and Hindu Indian patients, populations in whom the allele is prevalent (2%–20%), reflecting this strong association with ORs of 236 (95% CI: 72–778), 55 (18–168), 22 (4–12.70), and 71 (3–1689), respectively [41]. In

the European population, however, the frequency of HLA-B*15:02 is only 0.06%. A database search revealed that 2% of Spanish Romani people likely carry the risk variant HLA-B*15:02 [42], which is clearly higher than the frequency in the European population; in fact, our group published the first case of a Spanish Romani patient who developed SJS upon treatment with CBZ [43]. The same patient was a carrier of the HLA-C*08:01 allele as part of the ancestral haplotype (HLA-A*11:01, B*12:01, C*08:01). HLA-C*08:01 was not observed in any CBZ-tolerant patient, and the general population allele frequency was 0.2%. An association between CBZ-induced SCAR and HLA-A*31:01, first reported in Han-Chinese patients [44], and more recently in the European population, was reported [45]. Nonetheless, HLA-B*15:02 is strongly associated with a risk of SJS/TEN, whereas HLA-A*31:01 shows a strong association with CBZ-induced DRESS in Europeans ($p < 0.001$; OR 57.6; 95% CI: 11.0–340), and in the Chinese ($p < 0.001$; OR 23.0; 95% CI: 4.2–125). However, HLA-A*31:01 had no association with CBZ-SJS/TEN in the Chinese and only a weak association was detected in Europeans [46]. Our results are in agreement with these previous studies. We identified significant associations between HLA carriers in CBZ-induced SJS/TEN that are different from those detected for CBZ-induced DRESS. To our knowledge, it is the first time that a strong association between HLA-A*11:01 and CBZ-induced SJS/TEN was found, even though the number of cases was small in the present study.

This study has several limitations. One limitation was the small number of patients included per drug and entity; therefore, only strong associations (OR > 5) could be detected. It is possible that the statistical data are difficult to reproduce in similar populations because of the rarity of certain genetic polymorphisms, although this possibility is not high given the concordance of the statistical results with the 3 control groups. Another limitation could be the appropriateness of using patients awaiting haematopoietic stem cell transplantation as controls who are representative of the general Spanish population. The objective of Balas et al. [19] study was to predict the chance of other patients finding a suitable unrelated donor, as well as to improve search strategies. Other studies attempted to study the frequencies of HLA haplotypes by regions instead of alleles to evaluate the availability of matched donors of the same population [47,48]. Although 2 cases have been described of somatic mutations in the HLA-A or HLA-B genes, respectively, in the tumour cells of two patients with acute myelogenous leukaemia, these results can be detected by discrepant results in the expression of the allele [49,50].

The results of pharmacogenomic studies could have an important impact on the prevention of SCAR. Some HLA carriers associated with the risk of SCARs without evidence of hypersensitivity reactions exist in tolerant control groups (except HLA-B*38:01). This fact is consistent with the evidence that AED stimulates an antigen-specific HLA restricted CD4+ CD8+ T cell response and that a suitable HLA is necessary, but not sufficient by itself, for a hypersensitivity reaction. In addition, the cost of screening for genetic risk factors before prescribing AED must be estimated.

5. Conclusions

We have identified significant associations between AED-induced SJS/TEN that are different from those found for AED-induced DRESS. We also identified several significant genetic risk factors for AED-induced SJS/TEN or DRESS for the first time in the Spanish Caucasian population: The simultaneous presence of HLA-A*02:01 and Cw*15:02 as a risk factor for PHT-induced SJS/TEN, HLA-A*11:01 for CBZ-induced SJS/TEN, HLA-B*38:01 for LTG- and PHT- induced SJS/TEN, and HLA-A*24:02 for LTG- and PHT- induced DRESS. The strong association between HLA*31:01 and CBZ-DRESS in Europeans was confirmed in this study.

Financial & competing interests disclosure

The study was supported by research grants from EC10-349, FIS PI122/02267 and FIS PI13/01768 from the Instituto de Salud Carlos III – Ministerio de Economía y Competitividad (co-founded by FEDER). The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

Contributorship

Program concept and design: ER, TB, JF.

Data acquisition and entry: VL, MAMH, RC, AF, JGR, RH, LC, HYT, JAA, CGH.

Analysis and interpretation of data were carried out by OL, OG, JAA, HYT, AMB, VL, PH, and verified by JLC, AJC, RH, and FJA.

Drafting of the manuscript: ER, TB, HYT, AMB, FJA.

Critical revision of the manuscript for important intellectual content: ER, TB, JF.

Acknowledgements

We are grateful to other members of the PIEL*enRed* consortium for their contribution to this work. The authors would like to thank Antonio Balas for the advice on the haplotype population. The authors would like to thank Juliette Siegfried and her team at ServingMed.com for their editing of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.phrs.2016.11.027.

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