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An update on HLA alleles as pharmacogenetic markers for antiepileptic drug-induced cutaneous adverse reaction

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ABSTRACT: Epilepsy is a common neurological disorder affecting approximately 50 million people worldwide. Antiepileptic drugs (AEDs) are commonly used to treat the disease depending, mainly on the type of seizure. However, the use of AEDs may also lead to cutaneous adverse drug reactions (cADR) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), exfoliative dermatitis (ED) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS), which are unwanted comorbidities in epilepsy. It was first discovered that the HLA-B*15:02 allele was strongly associated with carbamazepine (CBZ)-induced SJS/TEN among Han Chinese and this led to the discovery of other HLA alleles and cytochrome P450 (CYP) genes that were significantly associated with various AED-induced cADRs across various populations. This mini-review is an update on the latest findings of the involvement of various HLA alleles and CYP alleles in cADRs caused by CBZ, phenytoin (PHT), oxcarbazepine (OXC) and lamotrigine (LTG) in different case-control studies around the world. From our review, we found that CBZ- and PHT-induced cADRs were more commonly reported than the other AEDs. Therefore, there were more robust pharmacogenetics studies related to these AEDs. OXC- and LTG-induced cADRs were less commonly reported, and so more studies are needed to validate the reported association of the newer reported HLA alleles with these AEDs. It is also important to consider the allelic frequency within a given population before concluding the use of these alleles as genetic markers to prevent AED-induced cADR. Overall, the current body of research point to a combination of alleles as a better pharmacogenetic marker compared to the use of a single gene as a genetic marker for AED-induced cADR.

Keywords: pharmacogenetic marker; HLA alleles; antiepileptic drugs; AEDs; cutaneous adverse drug reaction; cADR;

1. INTRODUCTION

The World Health Organisation (WHO) states that epilepsy is the most common chronic neurological disorder, affecting an estimated 50 million people worldwide. Generally, the incidence of epilepsy in developed countries is estimated to be 50 per 100,000 (range 40−70 per 100,000/year) [1] while the epilepsy incidence in resource-poor countries is around 100−190 per 100,000/year [2]; The most recent systematic review provided a better estimate of a pooled incidence rate of epilepsy at 61.44 per 100,000 person-years (95% CI 50.75-74.38) [3]. Epilepsy is defined as recurrent unprovoked seizures, and there are different categories of seizures [4]. A systematic review has shown that focal seizures predominate in the population of most countries compared to generalised seizure [5]. Antiepileptic drugs (AEDs) are drugs used for the management of seizures. Carbamazepine (CBZ), lamotrigine (LTG) and sodium valproate (SVA) are usually used as first-line treatment of focal seizures and generalized tonic-clonic seizures, however SVA is not advisable for girls or women due to its documented teratogenic effects and effects on the developing brain of children born to women taking SVA [6]. LTG is one of the first line AEDs for absence seizures. Phenytoin (PHT) is usually prescribed as a second line drug for focal and generalised seizure. However, it is not helpful for myoclonus or absence seizures [6]. It is not surprising, therefore, that the high usage of CBZ, LTG, PHE and SVA among epilepsy patients could incur a high incidence of cutaneous adverse drug reactions (cADRs). These include severe cutaneous adverse reaction (SCAR) such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS) and milder forms of adverse reaction such as exfoliative dermatitis (ED) and drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) and and maculopapular eruption (MPE), which are unwanted comorbidities in epilepsy [7].

SJS and TEN are usually considered as one disease entity and the classification is based on the extensiveness of the skin detachment and erosion of the mucous membrane, with 10% or less of epidermis detachment of the body surface area (BSA), 10-30% of BSA for SJS/TEN overlap and more than 30% of skin detachment of the BSA as shown in Figure 1 [8]. The clinical features of SJS and TEN include an initial acute phase characterised by non-specific symptoms such as fever, stinging eyes and discomfort upon swallowing, which precedes the cutaneous manifestation involving the trunk, face, palm and soles. In addition, erythema and erosion of the buccal, genital and/or ocular mucosa occur in 90% of patients. In some cases, the gastrointestinal and respiratory tracts are also affected [9,10]. The second stage of the acute phase involves large areas of epidermal detachment, and the extent of the detachment is a major prognostic factor. In the late stage of TEN, 62.5% of patients suffer from hyper or hypopigmentation, and 37.5% suffer from nail dystrophies and ocular complications [11]. The severity of SJS and TEN can lead to mortality, with a 5% mortality rate for SJS and up to 30% mortality rate for TEN [12]. This is one of the comorbidities that could affect epilepsy patients taking AEDs. A recent analysis of the US Food and Drug Administration (FDA) adverse event reporting showed that the use of AEDs posed a significantly higher risk of SJS/TEN compared to non-AEDs. They reported that AEDs as a class had an odds ratio (OR) of 8.7 (95% CI 7.5-10.2) and a proportional reporting ratio (PRR) of 8.7 (95% CI 7.5-10.2) for SJS/TEN [13]. Another recent study also showed an increased risk of SJS/TEN due to CBZ, PHT and LTG among new users [14,15]. Frey et al. reported substantially increased ORs for CBZ (OR 92.27, 95% CI 16.83 -∞), LTG (OR 49.96, 95% CI 10.13-∞), PHT (OR 26.90, 95% CI 4.88-∞), and SVA (OR 10.51, 95% CI 1.25-∞) [14].

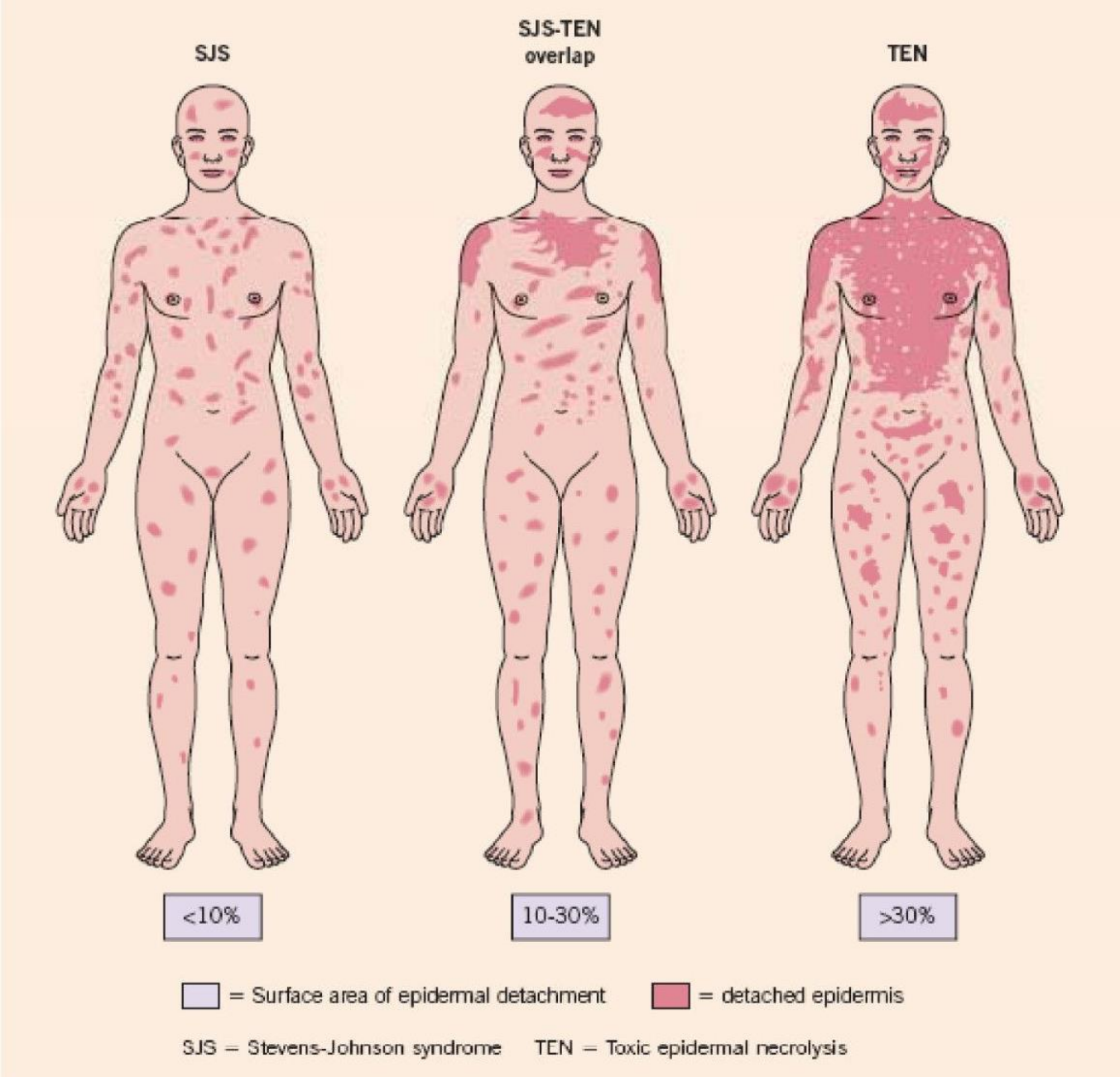

Figure 1: Pictorial representation of the distribution of epidermal detachment for SJS, SJS/TEN and TEN. The figure is reproduced without any modifications from [8] under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0). The figure was originally adapted from [16] by [8].

One of the earliest pharmacogenetic markers for AED-induced cADRs is the strong association of HLA-B*15:02 with a higher risk of CBZ-induced SJS/TEN among the Han Chinese population in Taiwan [17,18]. This was further validated in other Han Chinese populations in Hong Kong [19] and different regions of mainland China [20-22]. Other populations that were also reported to have a similar association of HLA-B*15:02 with CBZ-induced SJS/TEN include Thailand [23-25], Malaysia [26,27], Singapore [28], Vietnam [29] and northern India [30]. However further investigation in other countries showed that HLA-B*15:02 is not a universal marker for CBZ-induced SJS/TEN for populations with a low allelic frequency of HLA-B*15:02, such as Caucasians [31-33], Japanese [34-36] and South Koreans [37,38]. These population, however, demonstrated that another HLA

allele, HLA-A*31:01 is associated with CBZ-induced SJS/TEN instead of HLA-B*15:02. This review is an update on the current development of genetic markers for AED-induced cADR.

2. THE ASSOCIATION OF HLA-B*15:02 AND OTHER HLA ALLELES WITH CARBAMAZEPINE-INDUCED cADR

Chung et al. (2004) [17] first reported the association of HLA-B*15:02 with CBZ-induced SJS/TEN with an OR of 2504 (95% CI, 125-109) among the Han Chinese population in Taiwan. They were abrupt in confirming this association with a larger cohort of patients (OR of 1357 95% CI, 193.4-8838.3; P_c=1.6×10^{-41}) [18]. This was further validated in other Han Chinese populations in Hong Kong with a significant association of the HLA-B*15:02 allele with SJS/TEN induced by CBZ, PHT and LTG (OR of 17.6, 95% CI 2.9-105.2; *P*=0.001), but not with maculopapular exanthema (MPE) (*P*=0.32) [19]. Similar studies in the central [20], southern [21], and southwestern [22] regions of China also confirmed the association of HLA-B*15:02 with CBZ-induced SJS/TEN. In northeastern China, the association of HLA-B*15:02 with CBZ-induced SJS was weaker, at only 22.9% (OR=18.222, 95% CI 3.662-90.662), thus disputing the routine use of HLA-B*15:02 as a general marker for CBZ-induced SJS/TEN among Han Chinese. The authors concluded that due to the low frequency of HLA-B*15:02 among Han Chinese in the northeastern region of China, HLA-B*15:02 is unlikely to be a useful marker for CBZ-induced SJS [39]; their study suggested other HLA alleles as markers as stated in Table 1.

The association of HLA-B*15:02 with CBZ-induced SJS/TEN is also established in other populations such as Thai, Singaporean, Malaysian, Vietnamese and Northern Indian as shown in Table 1. Interestingly, Man et al. (2007) [19] was amongst the first to discover the association of other AEDs, PHT and LTG with HLA-B*15:02 and this has spurred other studies on the association of these AEDs with HLA-B*15:02, which will be discussed in a later section. In the Javanese and Sundanese population, 66.7% of patients with CBZ-induced SJS/TENs have HLA-B*15:02, interestingly they also found association of HLA-B*15:21 with the disease, and since both HLA-B*15:02 and HLA-B*15:21 are under the HLA-B75 serotype, they proposed HLA-B75 serotyping instead of screening individual alleles [40].

Lonjou et al. (2006) [31] reported that HLA-B*15:02 is not associated with CBZ-induced SJS/TEN amongst Caucasians, but only in 4 patients with Asian ancestry. Further studies in the UK also confirmed that HLA-B*15:02 is not associated with CBZ-induced SJS/TEN amongst self-reported Caucasian. However, they are unable to decipher what other HLA alleles might be involved in CBZ-induced SJS/TEN amongst Caucasians [32,33]. A large genome-wide association study (GWAS) of patients with European descent was able to uncover the presence of single nucleotide polymorphisms (SNPs) associated with CBZ-cADRs which corresponded to the region of the HLA-B*31:01 allele. Further analysis was able to demonstrate a significant association of HLA-A*31:01 with CBZ-induced SJS/TEN, as well as CBZ-induced hypersensitivity syndrome (HSS) and CBZ-induced MPE [41]. A similar GWAS amongst Japanese patients also demonstrated similar findings, with a high association of SNPs in the region of the HLA-A*31:01 allele, with 60.7% of CBZ-cADR (both DISH and SJS/TEN) patients (OR of 10.8, 95% CI of 5.9-19.6; *P*=3.64 × 10^{-15}). To validate the GWAS findings, Ozeki et al. (2011) [42] performed a replication study with an independent Japanese case-control cohort and confirmed the association of HLA-A*31:01 with CBZ-cADR (OR of 9.5, 95% CI of 5.6-16.3; *P*=1.09×10^{-16}). A study of the Korean population reported that HLA-A*31:01 was associated with CBZ-induced DIHS while HLA-B*15:11 was associated with CBZ-induced SJS [38]. Another study suggested that HLA-B*15:11 was associated with CBZ-induced SJS/TEN in Japanese patients, although there is a need for a larger study to verify this [43]. The latest study with a larger cohort of CBZ-induced cADRs in Thailand was able to detect a significant association of HLA-B*15:02 and HLA-B*58:01 with CBZ-induced MPE patients, as well as an association of HLA-B*58:01 with CBZ-induced DRESS [43]. This study also confirmed the strong association of HLA-B*15:02 with CBZ-induced SJS as previously reported, as well as

Table 1. Compiled studies of associating alleles with antiepileptic drugs (AEDs)-related cutaneous adverse drug reactions (cADRs) across different populations.

Drug	HLA allele	Phenotype	Frequency	Population	P value	OR (95% CI) [case vs tolerant group]	Sample size	Ref.
CBZ	HLA-B*15:02	SJS	100%	Han Chinese (Taiwan)	3.13×10^{-27} *	2504 (125-109, 522)	CBZ-SJS (*n*=44); CBZ-tolerant (*n*=101); population control (*n* = 93)	[17]
		SJS/TEN	98.3%	Han Chinese (Taiwan)	1.6×10^{-41} *	1357 (193.4-8838.3)	CBZ-SJS/TEN (n=60); CBZ-HSS (n=13); CBZ-MPE (n=18); CBZ tolerant (n=144)	[18]
	HLA-A*31:01	MPE	33.3%	Han Chinese (Taiwan)	2.2×10^{-3} *	17.5 (4.6-66.5)		
CBZ	HLA-B*15:02	SJS/TEN	100%	Han Chinese (Hong Kong)	1.48×10^{-4} *	71.9 (3.7-1,415.8)	CBZ-SJS/TEN (n=4); PHT-SJS (n=1); LTG-TEN (n=1); PB-HSS (n=1); PHT-HSS (n=1), AED-MPE (n=16), AED-tolerant (n=48)	[19]
LTG *	HLA-B*15:02	SJS/TEN	100%	Han Chinese (Hong Kong)				
PHT *	HLA-B*15:02	SJS/TEN	100%	Han Chinese (Hong Kong)				
CBZ	HLA-B*15:02	SJS/TEN	100%	Han Chinese (central China)	≤0.05 *	184 (33.2-1021.0)	CBZ-SJS/TEN (n=8); CBZ-MPE (n=31); CBZ-tolerant (n=50); population control (n=71)	[20]
		SJS/TEN	100%	Han Chinese (southern China)	<0.001 *	114.826 (6.25-2,111.03)	CBZ-SJS/TEN (n=9); CBZ-MPE (n=39); CBZ-tolerant (n=80); population control (n=62)	[21]
		SJS/TEN	94.11%	Han Chinese (southwestern China)	<0.0001 *	152 (12 -1,835)	CBZ-SJS/TEN (n=17); CBZ-tolerant (n=21), population control (n=185)	[22]
		SJS/TEN	22.9%	Han Chinese (northeastern China)	0.000 *	18.222 (3.66-90.66)	CBZ-SJS (n=35); CBZ-tolerant (n=125)	[39]
	HLA-A*31:01	SJS/TEN	35%	Han Chinese (northeastern China)	0.000 *	12.923 (3.58-46.59)		
	HLA-B*58:01	SJS/TEN	20%	Han Chinese (northeastern China)	0.013 *	4.958 (1.26-19.49)		
	HLA-C*03:02	SJS/TEN	20%	Han Chinese (northeastern China)	0.013 *	4.958 (1.26-19.49)		
	DQB1*03:03	SJS/TEN	40%	Han Chinese (northeastern China)	0.022 *	3.121 (1.14-8.54)		
	DRB1*07:01	SJS/TEN	35%	Han Chinese (northeastern China)	0.003 *	4.639 (1.57-13.71)		
	HLA-B*15:02	SJS	100%	Thai	0.0005 *	25.5 (2.68-242.61)		[23]

PHT	HLA-B*15:02	SJS	100%	Thai	0.005 *	18.5 (1.82-188.40)	CBZ-SJS (n=6); PHT-SJS (n=4); AED-induced MPE (n=21); AED-tolerant (n=50)	
CBZ	HLA-B*15:02	SJS/TEN	88.1%	Thai	2.89×10^{-12} *	54.76 (14.62-205.13)	CBZ-SJS/TEN (n=42); CBZ-tolerant (n=42)	[24]
		SJS/TEN	94.1%	Thai	<0.001 *	75.4 (13.0-718.9	CBZ-SJS/TEN (n=34), CBZ-tolerant (n=40)	[25]
		SJS/TEN	75%	Thai	4.46×10^{-13} *	70.91 (19.67-255.65)	CBZ-SJS/TEN (n=16); CBZ-MPE (n=17); CBZ-DRESS (n=5); CBZ-tolerant (n=271); population control (n=470)	[44]
	HLA-B*15:21	SJS/TEN	12.5%	Thai	0.013 *	9.54 (1.61-56.57)		
	HLA-B*15:02	MPE	23.52%	Thai	0.002 *	7.27 (2.04-25.97)		
	HLA-B*58:01	MPE	29.41%	Thai	0.007 *	4.74 (1.53-14.66)		
		DRESS	40%	Thai	0.032 *	7.55 (1.20-47.58)		
	HLA-B*15:02	SJS/TEN	75%	Malaysians	7.87×10^{-6} #	16.15 (4.57-62.4)	CBZ-SJS/TEN (n=21); population control (n=300)	[26]
	HLA-A74	SJS/TEN	18.8%	Malaysians		13.62 (2.93-63.2)		
	HLA-B*15:02	SJS/TEN	100%	Malaysians	0.0003 *	N.R.	CBZ-SJS/TEN (n=6); CBZ-rash (n=2); PHT-rash (n=2), AED-tolerant (n=8)	[27]
		SJS/TEN	100%	Singaporeans	N. R.	27.20 (2.67 to ∞)	CBZ-SJS/TEN (n=5); CBZ-HSS (n=6); CBZ-tolerant (n=10)	[28]
		SJS/TEN	89.5%	Vietnamese	<0.0001 *	33.78 (7.55-151.03)	CBZ-SJS/TEN (n=35); CBZ-DRESS (n=3); CBZ-tolerant (n=25)	[29]
		SJS/TEN	66.7%	Indonesians	0.029 *	6.5 (1.2-33.57)	CBZ-SJS/TEN (n=12); CBZ-tolerant (n=17)	[40]
	HLA-B*15:21	SJS/TEN	16.7%	Indonesians	0.55 *	3.2 (0.26-40.05)		
	HLA-B*15:02	SJS/TEN	75%	Indians	0.0014 *	71.40 (0-1698)	CBZ-SJS/TEN (n=8), normal subjects (n=10)	[30]
		SJS/TEN	(16.7%-only in patients with Asian ancestry)	United Kingdom (UK)	N. R.	N.R.	CBZ-SJS/TEN (n=12)	[31]
	HLA-A*31:01	SJS/TEN	42%	European	8.0×10^{-5} *	25.93; (4.93 to 116.18)	CBZ-SJS/TEN (n=12); CBZ-HSS (n=26); CBZ-MPE (n=43); CBZ-tolerant (n=257); population control (n=3987)	[41]
		HSS	40%	European	0.03 *	12.41 (1.27 to 121.03)		
		MPE	21.7%	European	8.0×10^{-7} *	8.33 (3.59-19.36)		
		SJS/TEN	83.3%	Japanese	2.35×10^{-4} *	33.9 (3.9-295.6)	CBZ-SJS/TEN (n=6); CBZ-HSS (n=36); CBZ-tolerant (n=420)	[42]
		HSS	58.3%	Japanese	2.06×10^{-9} *	9.5 (4.6-19.5)		
	HLA-A*15:11	SJS/TEN	14.3%	Japanese	0.0004 #	16.3 (4.76-55.6)	CBZ-SJS/TEN (n=28); normal subjects (n=493)	[43]
	HLA-B*15:11	SJS	42.9%	Korean	0.011 *	18.0 (2.3-141.2)	CBZ-SJS (n=7); CBZ-HSS (n=17); CBZ-tolerant (n=50)	[38]
	HLA-A*31:01	HSS	58.8%	Korean	0.001 *	8.8 (2.5-30.7)		

PHT	CYP2C9*3	cADR (not specified)	30%	Korean	0.007 *	167 (N.R.)	PHT-cADR (n=10); PHT-tolerant (n=40); population control (n=58)	[45]
	HLA-B*15:02	SJS/TEN	30.8%	Han Chinese (Taiwan)	0.0041 *	5.1 (1.8-15.1)	PHT-SJS/TEN (n=26); LTG-SJS/TEN (n=6); OXC-SJS (n=3); PHT-tolerant (n=113); LTG-tolerant (n=67); population control (n=93)	[46]
	HLA-B*13:01	SJS/TEN	34.6%	Han Chinese (Taiwan)	0.0154 *	5.1 (1.8-15.1)		
	Cw*0801	SJS/TEN	34.6%	Han Chinese (Taiwan)	0.0281 *	3.0 (1.1-7.8)		
	DRB1*1602	SJS/TEN	26.9%	Han Chinese (Taiwan)	0.0128 *	4.3 (1.4-12.8)		
OXC	HLA-B*15:02	SJS/TEN	100%	Han Chinese (Taiwan)	8.4×10^{-4} #	80.7 (3.8-1714.4)		
LTG	HLA-B*15:02	SJS/TEN	33%	Han Chinese (Taiwan)	0.1266 *	5.1 (0.8-33.8)		
PHT	HLA-A*33:03	SJS/TEN	30.77%	Thai	0.0495 *	2.70 (1.10-6.63)	PHT-SJS/TEN (n=39); PHT-DRESS (n=21); PHT-tolerant (n=92)	[47]
	HLA-B*38:02	SJS/TEN	20.51%	Thai	0.0281 *	3.70 (1.19-11.51)		
	HLA-B*51:01	SJS/TEN	17.95%	Thai	0.0163 *	4.81 (1.32-17.54)		
		DRESS	19.05%	Thai	0.0381 *	5.18 (1.18-22.74)		
	HLA-B*56:02	SJS/TEN	10.26%	Thai	0.0274 *	10.40 (1.12-96.31)		
	HLA-B*58:01	SJS/TEN	23.08%	Thai	0.0431 *	3.15 (1.11-8.91)		
	HLA-C*14:02	SJS/TEN	17.95%	Thai	0.0077 *	6.49 (1.59-26.62)		
	CYP2C9*3	SJS/TEN	23.08%	Thai	0.0133 *	4.30 (1.41-13.09)		
		SJS/TEN	20.0%	Thai	0.0251 *	5.70 (1.39-23.36)	PHT-SJS/TEN (n=15); PHT-tolerant (n=100); population control for HLA alleles (n=758); population controls for CYP alleles (n=250)	[48]
	HLA-B*13:01	DRESS	52.4%	Thai	0.0003 *	6.76 (2.42-18.85)		
	HLA-B*56:02/04	DRESS	14.3%	Thai	0.0046 *	38.03 (1.88-767.19)		
	CYP2C19*3	DRESS	19.0%	Thai	0.0478 *	4.47 (1.09-18.36)		
	HLA-B*15:02	DRESS	18.0 % (tolerant group)	Thai	0.0402 *	0.10 (0.01-1.79)		
	CYP2C9*3	SJS/TEN	41.70%	Han Chinese (Taiwan)	1.2×10^{-10} *	30.0 (8.4-109)	PHT-SJS/TEN (n=48); PHT-DRESS (n=42); PHT-MPE (n=78) PHT-tolerant (n=130); population control (n=41)	[49]
	HLA-B*15:02	SJS/TEN	27.1%	Han Chinese (Taiwan)	7.0×10^{-4} *	5.0 (2.0-13)		
	CYP2C9*3	DRESS	31.0%	Han Chinese (Taiwan)	7.0×10^{-7} *	19.0 (5.1-71)		
		MPE	11.5%	Han Chinese (Taiwan)	0.011 *	5.5 (1.5-21)		
		SJS/TEN	22.0%	Japanese	1.2×10^{-3} #	10.0 (3.4-32)	PHT-SJS/TEN (n=9); population control (n=2869)	
		SCAR	17.0%	Malaysians	0.048 #	6.9 (1.4-34)	PHT-SJS/TEN (n=4); population control (n=374)	
PHT	HLA-B*15:02	SJS/TEN	31.0%	Han Chinese (Taiwan)	1.73×10^{-7} *	6.52 (3.34-12.73)	PHT-SJS/TEN (n=65); PHT-DRESS (63); PHT-MPE (n=107); PHT-tolerant (n=367);	[50]
	HLA-B*:13:01	DRESS	29.0%	Han Chinese (Taiwan)	3.38×10^{-4} *	3.46 (1.82-6.55)		
		SCAR+MPE	21.0%	Han Chinese (Taiwan)	5.35×10^{-4} *	2.28 (1.44-3.59)		
	HLA-B*51:01	SCAR+MPE	16.0%	Han Chinese (Taiwan)	6.40×10^{-4} *	3.62 (2.03-6.46)		
	CYP2C9*3	SJS/TEN	34.0%	Han Chinese (Taiwan)	1.22×10^{-13} *	20.86 (9.03-48.20)		

		DRESS	27.0%	Han Chinese (Taiwan)	8.83×10^{-11} *	16.95 (6.93-41.47)		
		MPE	9.0%	Han Chinese (Taiwan)	0.003 *	4.20 (1.66-10.63)		
		SCAR+MPE	21.0%	Han Chinese (Taiwan)	4.66×10^{-14} *	10.74 (5.16-22.34)		
	CYP2C9*3/HLA-B*13:01/HLA-B*15:02/HLA-B*51:01	SJS/TEN	72%	Han Chinese (Taiwan)	1.77×10^{-15} *	9.82 (5.36-17.96)		
		DRESS	70%	Han Chinese (Taiwan)	3.83×10^{-13} *	8.05 (4.46-14.53)		
		MPE	45.0%	Han Chinese (Taiwan)	8.27×10^{-6} *	2.83 (1.80-4.44)		
		SCAR+MPE	60.0%	Han Chinese (Taiwan)	2.70×10^{-20} *	5.12 (3.59-7.31)		
PHT	HLA-B*15:02	SJS/TEN	61.5%	Malaysians (Malay)	0.016 *	5.71 (1.41-23.10)	PHT-SJS/TEN (n=13); PHT-DRESS (n=3) PHT-tolerant (n=32) ; population control (n=300)	[51]
	HLA-B*15:13	SJS/TEN	53.8%	Malaysians (Malay)	0.003 *	11.28 (2.25-59.6)		
		DRESS	100%	Malaysians (Malay)	0.003 *	59.0 (2.49-1395.74)		
	HLA-A*02:01/ HLA-Cw*15:02	SJS/TEN	16.7%	Spanish	0.009 #	14.75 (1.54-167.0)	PHT-SJS/TEN (n=9); LTG-SJS/TEN (n=3); CBZ-SJS/TEN (n=2); PHT-DRESS (n=5); LTG-DRESS (n=3); CBZ-DRESS (n=4); PHT-tolerant (n=28); LTG-tolerant (n=10); PHT-LTG-tolerant (n=38); CBZ-tolerant (n=28); AED-tolerant (n=61)	[52]
PHT-LTG	HLA-B*38:01	SJS/TEN	41.7%	Spanish	0.012 *	12.86 (1.66-123.82)		
	HLA-B*24:02	DRESS	75.0%	Spanish	0.003 *	22.56 (2.19-559.39)		
LTG	HLA-B*38:01	SJS/TEN	100%	Spanish	0.001*	147 (1.88-483)		
	HLA-B*24:02	DRESS	100%	Spanish	0.015 *	49.0 (1.25-46.13x10^{6})		
OXC	HLA-B*15:02	MPE	44.4%	Han Chinese (southwestern China)	0.011 #	8.8 (1.853-41.790)	OXC-MPE (n=9); OXC-tolerant (n=9); population control (n=72)	[53]
	HLA-B*13:02	MPE	14.3%	Han Chinese (southern)	0.001 #	7.83 (2.32-26.41)	OXC-MPE (n=14); OXC-tolerant (n=35); population control-southern Han Chinese (n=264); population control-Hong Kong Chinese population (n=569); population control-Guangzhou Han Chinese population (n=106)	[54]
	HLA-B*40:02	MPE	25%	Koreans	0.018 *	4.33 (1.36-13.79)	OXC-MPE (n=40); OXC-tolerant (n=70); Population control (n=485)	[55]
	DRB1*04:03	MPE	17.5%	Koreans	0.003 *	14.64 (1.73-123.90)		
	HLA-B*15:02	MPE	22.9% (tolerant group)	Koreans	0.016 *	0.18 (0.04-0.82)		
	HLA-B*15:02	SJS/TEN MPE	70.6%	Han Chinese (Taiwan)	1.87×10^{-10} *	27.90 (7.84-99.23)	OXC-SJS (n=20); OXC-DRESS (n=6); OXC-MPE (n=21); OXC-tolerant (n=101)	[56]
	HLA-B*15:02	SJS/TEN		Thai	2.65×10^{-3} *	49.00 (2.39-1006.00)	OXC-SJS (n=3); OXC-MPE (n=1); population control (n=99)	
LTG	HLA-A*02:02/HLA-B*35:01/HLA-C*04:01	MPE	25.0%	Mexican Mestizo	0.0009 *	18.33 (1.99-169.08)	LTG-SJS/TEN (n=4); LGT-MPE (n=10); CBZ-MPE (n=5); PHT-MPE (n=2); LTG-tolerant (n=28); CBZ-tolerant (n=18);	[57]
CBZ	HLA-A*01:01	MPE	30%	Mexican Mestizo	0.028 *	7.29 (1.02-52.01)		

	HLA-A*31:01	MPE	20%	Mexican Mestizo	0.04 #	4.64 (0.93-23.11)	PHT-tolerant (n=5); population control (n=225)	
PHT	HLA-C*08:02	MPE	75%	Mexican Mestizo	0.002 #	48.92 (4.92-486.80)		
LTG	HLA-A*24:02	MPE	71.4%	Korean	0.025 *	4.09 (1.22-13.69)	LTG-MPE (n=21); LTG-tolerant (n=29)	[58]
	HLA-A*24:02/Cw*01:02	MPE	47.6%	Korean	0.007 *	7.88 (1.81-34.28)		
	HLA-Cw*07:02	MPE	33.3%	Korean	0.034 #	2.82 (1.10-7.23)		
	HLA-A*33:03	MPE	28.9 % (population control)	Korean	0.012 #	0.12 (0.02-0.93)		
	HLA-A*02:07	MPE	70%	Thai	0.005 *	8.27 (1.83-37.41)	LTG-SJS (n=4); LTG-DRESS (n=1); LTD-MPE (n=10); LTG-tolerant (n=50); population control (n=986)	[59]

Keys: The AEDs included in the table are carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC), lamotrigine (LTG), with the associating severe cutaneous adverse reactions (SCARs): Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and less severe reactions: drug-induced hypersensitivity syndrome/ hypersensitivity syndrome (DIHS/HSS), drug reaction with eosinophilia and systemic symptoms (DRESS) and maculopapular eruption (MPE).

* case vs AED-tolerant group (significant when compared with AED-tolerant group and population)

case vs population control (only significant when compared with population control)

another allele, HLA-B*15:21 with CBZ-induced SJS/TEN [44]. The latest update on HLA typing that is significantly associated with CBZ-induced cADRs has painted a complex interplay of various HLA alleles in the disease as detailed in Table 1 besides HLA-B*15:02.

3. THE ASSOCIATION OF CYP2C9*3 AND HLA ALLELES WITH PHENYTOIN-INDUCED cADR

PHT is another AED that is commonly prescribed to epileptic patients and may cause cADR. PHT-induced cADR was first reported in 2004 to be significantly associated with the cytochrome P450 allele, CYP2C9*3 [45] as 90% of the drug is metabolised by the CYP2C9 enzyme in the liver [60]. Depondt et al. (2011) [61] also reported a similar association of CYP2C9*2 and CYP2C9*3 alleles with PHT-induced cADR (P_c=0.008). Both of these studies did not specify the type of cADR in their analysis. Association of HLA-B*15:02 with PHT-induced SJS/TEN was first reported alongside CBZ-induced SJS/TEN in Han Chinese from Hong Kong (1/1) [19], followed by Taiwan (8/26) [46] and Thai (4/4) [23]. Besides HLA-B*15:02, Hung et al. (2010) [46] also reported other HLA alleles that have a significant association with PHT-induced SJS/TEN, such as HLA-B*13:01, Cw*08:01 and DRB1*16:01. However, due to the small sample sizes, these studies needed replication. In a case-control study of 39 SJS/TEN, 21 DRESS and 92 phenytoin-tolerant patients, Tassaneeyakul et. al (2016) [47] reported that 6 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 the HLA-B*51:01 was significantly associated with phenytoin-related DRESS. The ORs of phenytoin-related SJS/TEN in the patients who carried one of these alleles ranged from 4-10 folds (refer to Table 1). CYP2C9*3 was reported to be significantly associated with PHT-induced SJS/TEN, with an OR of 4.30 (95% CI 1.41-13.09; *P*<0.05). For this study, interestingly there was no significant association of HLA-B*15:02 with PHT-induced SJS/TEN or PHT-induced DRESS as the frequencies of patients who carried the HLA-B*15:02 in the SJS/TEN (12.82%) or the DRESS (9.52%) groups were not significantly different from that of the PHT-tolerant controls (14.13%) [47]. Another Thai study looked at different HLA alleles and CYP alleles in PHT-associated cADR cases. Their multiple logistic regression analysis found that HLA-B*13:01, HLA-B*56:02/04, CYP2c19*3 and co-medication with omeprazole were strong risk factors for PHT-induced DRESS/DHS (adjusted OR of 13.29, *P*=0.0001; adjusted OR of 56.23, *P*=0.0007; adjusted OR of 6.75, *P*=0.0414; adjusted OR of 9.21, *P*=0.0020 respectively). As for PHT-induced SJS/TEN, the CYP2C9*3 allele and having Chinese ancestry were significant risk factors (adjusted OR of10.41, *P*=0.0042 and adjusted OR of 5.40, *P*=0.0097, respectively). For this study, the carrier rate for HLA-B*15:02 was found to be higher in SJS cases compared to the tolerant group and population control, but was not statistically significant. Interestingly, HLA-B*15:02 was found to be a protective factor in PHT-induced DRESS with OR of 0.10 (95% CI 0.01-1.79; *P*=0.0402) [48].

Using GWAS, Chung et al. in 2014 [49] was able to demonstrate a strong association of both CYP2C9*3 and HLA-B*15:02 with PHT-induced SJS/TEN amongst Taiwanese Han Chinese patients. CYP2C9*3 has a strong association with PHT-induced SJS/TEN and PHT-induced DRESS and a moderate association with PHT-induced MPE (refer to Table 1). The CYP2C9*3 allele is also shown to be a risk carrier gene for PHT-induced SJS/TEN in Malaysian and Japanese cohorts. The meta-analysis of the three cohorts showed a pooled OR of 12 (95% CI, 6.4-22; *z*=7.82; *P* < .00001) for a CYP2C9*3 association with phenytoin-related SJS-TEN, a pooled OR of 9.2 (95% CI, 4.3-20; *z*=5.70; *P* < .00001) for a CYP2C9*3 association with phenytoin-related DRESS, and an overall OR of 11 (95% CI, 6.2-18; *z*=8.58; *P* < .00001) for a CYP2C9*3 association with phenytoin-related sADR in these three populations. However, the frequency of HLA-B*15:02 is not as obvious, at 27.1% in PHT-induced SJS/TEN patients (OR of 5.0, 95% CI of 2.0-13; *Pc*=0.025) [49]. A recent study of ethnic Malays in Malaysia confirmed the association of HLA-B*15:02 with PHT-induced SJS/TEN, being positive in 61.5% of SJS/TEN cases (8/13) compared to 21.9% in controls (7/32); with

OR of 5.71, (*P*=0.016) compared with PHT-tolerant controls. The study also reported another novel HLA allele, the HLA-B*15:13 that was significantly associated with PHT-induced SJS/TEN, being positive in 53.8% of the SJS/TEN cases (7/13) with an OR of 11.28 (*P*=0.003) and all 3patients with PHT-DRESS with an OR of 59.00 (*P*=0.003) when compared with PHT-tolerant controls, with only 9.4% (3/32) positive cases [51]. Among the Caucasian population, a Spanish study showed that concomitant HLA-A*02:01/Cw15:02 alleles were significantly associated with PHT-SJS/TEN, with OR of 14.75, (*P*=0.009) compared to the AED-tolerant control group in a Caucasian population [52]. Table 1 shows a detailed description of the studies mentioned earlier. Each of these predisposing alleles for phenytoin-cADR accounts for up to only 30% of cases. Therefore, the currently available data suggest that the association of HLA alleles with the incidence of PHT-related cADR is only moderate and considerably weaker compared to HLA-B*15:02 and HLA-A*31:01 in CBZ-induced SJS/TEN. This led to the latest combined study of Han Chinese, Japanese and Thai patients by Su et al. [50]. They demonstrated that concurrent testing of CYP2C*3/ HLA-B*13:01/ HLA-B*15:02/ HLA-B*51:01 increased the sensitivity of the pharmacogenetic testing from 16.41% up to 71.88% with an OR of 8.88 (95% CI of 5.63-14.01; $P=2.12 \times 10^{-23}$) in the Taiwanese Han Chinese cohort. The meta-analysis of the three population groups showed that the four combined risk alleles have significant associations with PHT-cADR with an overall OR 4.55 (95% CI 1.44-14.41; z=2.58; *P*=0.01) [50]. With regards to PHT-associated cADR, current knowledge gleaned thus far points to the use of multiple predisposing alleles to improve the usefulness of predictive genetic testing before the prescription.

4. ASSOCIATION OF HLA ALLELES WITH OXCARBAZEPINE-INDUCED cADR

Oxcarbazepine (OXC) was developed as a second-generation AED. It is a 10-keto analogue of CBZ, with similar clinical efficacy as CBZ but with less severe adverse effects, as it is metabolised differently compared to CBZ [62]. Although the incidence of SJS/TEN induced by OXC is lower compared to CBZ, there have been reports of OXC-induced cADR [63]. OXC-induced SJS/TEN was first observed to have a strong association with HLA-B*15:02 in Han Chinese [46], being positive in all three cases of OXC-induced SJS/TEN. Another study in central China also reported an association of HLA-B*15:02 with OXC-induced SJS/TEN for three patients [64]. Hu et al. (2011) [53] reported that OXC-induced MPE from southwest China was also associated with HLA-B*15:02, although only among 44.4% of the 9 patients, but the association was significant with an OR of 8.8; 95% CI of 1.853-41.790; *P*=0.011 (refer to Table 1). However, this study did not report the HLA genotype of the OXC-induced MPE that were negative for HLA-B*15:02 [53]. On the other hand, a slightly bigger study from southern China, however, reported that there was a statistically significant association between HLA-B*15:02 and OXC-induced MPE compared to the OXC-tolerant group. However another allele HLA-B*13:02 has shown significant association with OXC-induced MPE compared with the general population with OR of 7.83, 95% CI 2.32-26.41; *P*=0.001 [54]. Lv et al. also reported the lack of association of HLA-B*15:02 with OXC-induced MPE in patients of northern China, but the OXC-induced MPE was associated with HLA-B*38:02 [65]. Moreover, some case reports also reported that the genotyping of patients with OXC-induced SJS/TEN revealed its association with HLA-B*15:18 [66,67]. The latest study by Chen et al. (2017) [56] included the largest cohort to date, which addressed the role of HLA alleles in OXC-induced cADR. This study confirmed the strong association of HLA-B*15:02 with OXC-SJS/TEN in both Han Chinese and Thai patients (OR of 27.90; 95% CI 7.84-99.2; $P=1.87 \times 10^{-10}$) but did not find a significant association of HLA-A*31:01 with OXC-cADR [56]. A Korean study looked at OXC-induced MPE and found an association with HLA-B*40:02 (OR 14.64, 95% CI 1.73-123.90; *P*=0.003) and DRB1*04:03 (OR 0.18, 95% CI 0.04-0.82; *P*=0.016). Interestingly, this study also found that HLA-B*15:01 was a protective allele (OR of 0.18, 95% CI 0.04-0.82; *P*=0.016) [55]. From the studies done thus far, HLA-B*15:02 is strongly associated with both

OXC-induced SJS/TEN and OXC-induced MPE in populations with a high frequency of this allele. However, more studies are needed to establish the links of other HLA alleles with OXC-MPE in populations that have a low allelic frequency of HLA-B*15:02.

5. ASSOCIATION OF HLA ALLELES WITH LAMOTRIGINE-INDUCED cADR

LTG-induced SJS/TEN was also first reported to be associated with HLA-B*15:02 in Han Chinese patients [19,46]. However, another study reported the lack of association of HLA-B*15:02 with LTG-induced SCAR and MPE amongst Han Chinese population in the southern region of China [68]. A Thai study reported these HLA alleles that have a significant association with LTG-induced MPE: HLA-B*15:02, HLA-B*33:03, HLA-B*35:08 and HLA-B*44:03 with the ORs reported in table 1 [59]. There were a few studies in Korea looking at the association of HLA alleles with LTG-induced cADR. Park et al. (2015) [69] reported that in their cohort of patients, the HLA-B*44:03 is present in three out of five patients with LTG-induced SJS/TEN. However, their sample size was too small to draw any conclusions. They did a follow-up study with larger sample size and confirmed that HLA-B*44:02 may have an association with LTG-induced SJS/ TEN with an OR of 12.75 (95% CI 1.03-157.14; *P*=0.053) [70]. Another study that looked at the association of HLA genes with LTG-induced MPE reported a significant association of HLA-A*24:02, HLA-Cw*01:02 and HLA-Cw*07:02 with the disease (refer to Table 1). They also found that concomitant A*24:02 and Cw*01:02 alleles were significantly more frequent in the LTG-MPE group than in the LTG-tolerant group (OR of 7.88, 95% CI 1.81-34.28; *P*=0.007). HLA-A*33:03 was reported as a protective allele against LTG-induced MPE with an OR of 0.12 (95% CI 0.02-0.93; *P*=0.012) [58]. As regards the Caucasian population, McCormack et al. (2012) were not able to find a significant association of HLA-A*31:01 with LTG-induced cADR in their GWAS [71]. Meanwhile, Fricke-Galindo et al. (2014) [57] reported that the haplotype that included the alleles, HLA-A*02:01/ HLA-B*35:01/ HLA-C*04:01:01 was significantly associated with LTG-induced MPE in Mexican Mestizo patients, with an OR of 18.33; 95% CI 1.99-169.08, *P*=0.0009. As the incidence of LTG-induced cADR is lower compared to other AEDs, there is a need for a larger multicentre study to observe the effect of HLA alleles in LTG-induced cADR cases.

6. CONCLUSION

Established data pertaining to the association of HLA alleles with AED-induced cADR still need further refinement as this appears to depend on the frequencies of the alleles in question in a given population. Further research is needed to confirm the validity of newer HLA alleles reported in the literature. Screening of these susceptible HLA alleles prior to drug prescription, either as a single or multiplex gene detection is important to prevent the unwanted side effects of AEDs.

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References

1. Sander JW. The epidemiology of epilepsy revisited. *Curr Opin Neurol.* 2003; 16(2):165-170. https://doi.org/10.1097/01.wco.0000063766.15877.8e
2. Sander JW, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry.* 1996; 61(5):433-443. https://doi.org/10.1136/jnnp.61.5.433

3. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon C-S, Dykeman J, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology.* 2017; 88(3):296-303. https://doi.org/10.1212/WNL.0000000000003509
4. Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017; 58(4):512-521. https://doi.org/10.1111/epi.13709
5. Neligan A, Sander JW: The incidence and prevalence of epilepsy. In: From channels to commissioning: a practical guide to epilepsy. Edited by Rugg-Gunn FJ, Smalls JE. Lecture notes for the biannual epilepsy teaching weekend organised by the UK Chapter of International League against Epilepsy, 1987.
6. Nunes VD, Sawyer L, Neilson J, Sarri G, Cross JH. Diagnosis and management of the epilepsies in adults and children: summary of updated NICE guidance. *BMJ.* 2012; 344:e281. https://doi.org/10.1136/bmj.e281
7. Rzany B, Correia O, Kelly JP, Naldi L, Auqueir A, Stern R. Risk of Steven-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. *The Lancet.* 1999; 353:2190-2194. https://doi.org/10.1016/S0140-6736(98)05418-X
8. Harr T, French LE. Toxic epidermal necrolysis and Steven-Johnson syndrome. *Orphanet J Rare Dis.* 2010; 5:39. https://doi.org/10.1186/1750-1172-5-39
9. Revuz J, Penso D, Roujeau JC, Guillaume JC, Payne CR, Wechsler J, et al. Toxic epidermal necrolysis. Clinical findings and prognosis factors in 87 patients. *Arch Dermatol.* 1987; 123(9):1160-1165. https://doi.org/10.1001/archderm.1987.01660330071012
10. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxic epidermal necrolysis: a clinical classification. *J Invest Dermatol.* 1994; 102(6):28S-30S. https://www.ncbi.nlm.nih.gov/pubmed/8006430
11. Magina S, Lisboa C, Leal V, Palmares J, Mesquita-Guimarães J. Dermatological and ophthalmological sequels in toxic epidermal necrolysis. *Dermatology.* 2003; 207(1):33-36. https://doi.org/10.1159/000070938
12. Hsu D, Brieva J, Silverberg N, Silverberg J. Morbidity andmortality of Stevens-Johnson syndrome and toxic epidermal necrolysis in United States adults. *J Invest Dermatol.* 2016; 136(7):1387-1397. https://doi.org/10.1016/j.jid.2016.03.023
13. Borrelli EP, Lee EY, Descoteaux AM, Kogut SJ, Caffrey AR. Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: An analysis of the US Food and Drug Administration Adverse Event Reporting System. *Epilepsia.* 2018; 59(12):2318-2324. https://doi.org/10.1111/epi.14591
14. Frey N, Bodmer M, Bircher A, Rüegg S, Jick SS, Meier CR, et al. The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs. *Epilepsia.* 2017; 58(12):2178-2185. https://doi.org/10.1111/epi.13925
15. Syu FK, Pan HY, Chuang PC, Huang YS, Cheng CY, Cheng FJ. Incidence of Stevens-Johnson syndrome following combination drug use of allopurinol, carbamazepine and phenytoin in Taiwan: A case-control study. *J Dermatol.* 2018; 45(9):1080-1087. https://doi.org/10.1111/1346-8138.14528
16. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol.* 1993; 129(1):92-96. https://doi.org/10.1001/archderm.1993.01680220104023
17. Chung WH, Hung SI, Hong HS, Shih MS, Yang LC, Ho HC, et al. Medical genetics: a marker for Steven-Johnson syndrome. *Nature.* 2004; 428:486. https://doi.org/10.1038/428486a
18. Hung SI, Chung WH, Jee SH, Chen WC, Chang YT, Lee WR, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogen & Genom.* 2006; 16:297-306. https://doi.org/10.1097/01.fpc.0000199500.46842.4a

19. Man CBL, Kwan P, Baum L, Yu E, Lau KM, Cheng ASH, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia.* 2007; 45(5):1015-1018. https://doi.org/10.1111/j.1528-1167.2007.01022.x
20. Wu XT, Hu FY, An DM, Yan B, Jiang X, Kwan P, et al. Association between carbamazepine-induced cutaneous adverse drug reactions and the HLA-B*1502 allele among patients in central China. *Epilepsy Behav.* 2010; 19(3):405-408. https://doi.org/10.1016/j.yebeh.2010.08.007
21. Wang Q, Zhou JQ, Zhou LM, Chen ZY, Fang ZY, Chen SD, et al. Association between HLA-B*1502 allele and carbamazepine-induced severe cutaneous adverse reactions in Han people of southern China mainland. *Seizure.* 2011; 20(6):446-448. https://doi.org/10.1016/j.seizure.2011.02.003
22. Zhang Y, Wang J, Zhao LM, Peng W, Shen GQ, Xue L, et al. Strong association between HLA-B*1502 and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in mainland Han Chinese patients. *Eur J Clin Pharmacol.* 2011; 67(9):885-887. https://doi.org/10.1007/s00228-011-1009-4
23. Locharernkul C, Loplumlert J, Limotai C, Korkij W, Desudchit T, Tongkobpetch S, et al. Carbamazepine and phenytoin induced Steven-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia.* 2008; 49(12):2087-2091. https://doi.org/10.1111/j.1528-1167.2008.01719.x
24. Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Chen P, Lin SY, Chen WH, et al. Association between HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in a Thai population. *Epilepsia.* 2010; 51(5):926-930. https://doi.org/10.1111/j.1528-1167.2010.02533.x
25. Kulkantrakorn K, Tassaneeyakul W, Tiamkao S, Jantararoungtong T, Prabmechai N, Vannaprasaht S, et al. HLA-B*1502 strongly predicts carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Thai patients with neuropathic pain. *Pain Pract.* 2012; 12(3):202-208. https://doi.org/10.1111/j.1533-2500.2011.00479.x
26. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *Int J Dermatol.* 2011; 50(2):221-224. https://doi.org/10.1111/j.1365-4632.2010.04745.x
27. Then SM, Rani ZZ, Raymond AA, Ratnaningrum S, Jamal R. Frequency of the HLA-B*1502 allele contributing to carbamazepine-induced hypersensitivity reactions in a cohort of Malaysian epilepsy patients. *Asian Pac J Allergy Immunol.* 2011; 29(3):290-293. https://www.ncbi.nlm.nih.gov/pubmed/22053601
28. Chong KW, Chan DW, Cheung YB, Ching LK, Hie SL, Thomas T, et al. Association of carbamazepine-induced severe cutaneous drug reactions and HLA-B*1502 allele status, and dose and treatment duration in paediatric neurology patients in Singapore. *Arch Dis Child.* 2014; 99(6):581-584. https://doi.org/10.1136/archdischild-2013-304767
29. Nguyen DV, Chu HC, Phan MH, Craig T, Baumgart K, van Nunen S. HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac Allergy.* 2015; 5(2):68-77. https://doi.org/10.5415/apallergy.2015.5.2.68
30. Mehta TY, Prajapati LM, Mittal B, Joshi CG, Sheth JJ, Patel DB, et al. Association of HLA-B*1502 allele and carbamazepine-induced Stevens-Johnson syndrome among Indians. *Indian J Dermatol Venereol Leprol.* 2009; 75(6):579-582. https://doi.org/10.4103/0378-6323.57718
31. Lonjou C, Thomas L, Borot N, Ledger N, de Toma C, LeLouet H, et al. A marker for Stevens-Johnson syndrome ...: ethnicity matters. *Pharmacogenomics J.* 2006; 6(4):265-268. https://doi.org/10.1038/sj.tpj.6500356
32. Pirmohamed M, Arbuckle JB, Bowman CE, Brunner M, Burns DK, Delrieu O, et al. Investigation into the multidimensional genetic basis of drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics.* 2007; 8(12):1661-1691. https://doi.org/10.2217/14622416.8.12.1661
33. Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M. HLA-B locus in caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics.* 2006; 7:813-818. https://doi.org/10.2217/14622416.7.6.813

34. Kashiwagi M, Aihara M, Takahashi Y, Yamazaki E, Yamane Y, Song Y, et al. Human leukocyte antigen genotypes in carbamazepine-induced severe cutaneous adverse drug response in Japanese patients. *J Dermatol.* 2008; 35(10):683-685. https://doi.org/10.1111/j.1346-8138.2008.00548.x
35. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics.* 2008; 9(11):1617-1622. https://doi.org/10.2217/14622416.9.11.1617
36. Ikeda H, Takahashi Y, Yamazaki E, Fujiwara T, Kaniwa N, Saito Y, et al. HLA Class I markers in Japanese patients with carbamazepine-induced cutaneous adverse reactions. *Epilepsia.* 2010; 51(2):297-300. https://doi.org/10.1111/j.1528-1167.2009.02269.x
37. Kim SH, Ye YM, Palikhe NS, Kim JE, Park HS. Genetic and ethnic risk factors associated with drug hypersensitivity. *Curr Opin Allergy Clin Immunol.* 2010; 10(4):280-290. https://doi.org/10.1097/ACI.0b013e32833b1eb3
38. Kim SH, Lee KW, Song WJ, Jee YK, Lee SM, Kang HR, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res.* 2011; 97(1-2):190-197. https://doi.org/10.1016/j.eplepsyres.2011.08.010
39. He XJ, Jian LY, He XL, Wu Y, Xu YY, Sun XJ, et al. Association between the HLA-B*15:02 allele and carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Han individuals of northeastern China. *Pharmacol Rep.* 2013; 65(5):1256-1262. https://www.ncbi.nlm.nih.gov/pubmed/24399721
40. Yuliwulandari R, Kristin E, Prayuni K, Sachrowardi Q, Suyatna FD, Menaldi SL, et al. Association of the HLA-B alleles with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in the Javanese and Sundanese population of Indonesia: the important role of the HLA-B75 serotype. *Pharmacogenomics.* 2017; 18(18):1643-1648. https://doi.org/10.2217/pgs-2017-0103
41. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M, et al. HLA-A*3101 and Carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med.* 2011; 364:1134-1143. https://doi.org/10.1056/NEJMoa1013297
42. Ozeki T, Mushiroda T, Yowang A, Takahashi A, Kubo M, Shirakata Y, et al. Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet.* 2011; 20(5):1034-1041. https://doi.org/10.1093/hmg/ddq537
43. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia.* 2010; 51(12):2461-2465. https://doi.org/10.1111/j.1528-1167.2010.02766.x
44. Sukasem C, Chaichan C, Nakkrut T, Satapornpong P, Jaruthamsophon K, Jantararoungtong T, et al. Association between HLA-B Alleles and Carbamazepine-Induced Maculopapular Exanthema and Severe Cutaneous Reactions in Thai Patients. *J Immunol Res.* 2018; 2018:2780272. https://doi.org/10.1155/2018/2780272
45. Lee AY, Kim MJ, Chey WY, Choi J, Kim BG. Genetic polymorphism of cytochrome P450 2C9 in diphenylhydantoin-induced cutaneous adverse drug reactions. *Eur J Clin Pharmacol.* 2004; 60(3):155-159. https://doi.org/10.1007/s00228-004-0753-0
46. Hung SI, Chung WH, Liu ZS, Chen CH, Hsih MS, Hui RC, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics.* 2010; 11(3):349-356. https://doi.org/10.2217/pgs.09.162
47. Tassaneeyakul W, Prabmeechai N, Sukasem C, Kongpan T, Konyoung P, Chumworathayi P, et al. Associations between HLA class I and cytochrome P450 2C9 genetic polymorphisms and phenytoin-related severe cutaneous adverse reactions in a Thai population. *Pharmacogenet Genomics.* 2016; 26(5):225-234. https://doi.org/10.1097/FPC.0000000000000211

48. Yampayon K, Sukasem C, Limwongse C, Chinvarun Y, Tempark T, Rerkpattanapipat T, et al. Influence of genetic and non-genetic factors on phenytoin-induced severe cutaneous adverse drug reactions. *Eur J Clin Pharmacol.* 2017; 73(7):855-865. https://doi.org/10.1007/s00228-017-2250-2
49. Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA.* 2014; 312(5):525-534. https://doi.org/10.1001/jama.2014.7859
50. Su SC, Chen CB, Chang WC, Wang CW, Fan WL, Lu LY, et al. HLA Alleles and CYP2C9*3 as Predictors of Phenytoin Hypersensitivity in East Asians. *Clin Pharmacol Ther.* 2018. https://doi.org/10.1002/cpt.1190
51. Chang CC, Ng CC, Too CL, Choon SE, Lee CK, Chung WH, et al. Association of HLA-B*15:13 and HLA-B*15:02 with phenytoin-induced severe cutaneous adverse reactions in a Malay population. *Pharmacogenomics J.* 2017; 17(2):170-173. https://doi.org/10.1038/tpj.2016.10
52. Ramírez E, Bellón T, Tong HY, Borobia AM, de Abajo FJ, Lerma V, et al. 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. *Pharmacol Res.* 2017; 115:168-178. https://doi.org/10.1016/j.phrs.2016.11.027
53. Hu FY, Wu XT, An DM, Yan B, Stefan H, Zhou D. Pilot association study of oxcarbazepine-induced mild cutaneous adverse reactions with HLA-B*1502 allele in Chinese Han population. *Seizure.* 2011; 20(2):160-162. https://doi.org/10.1016/j.seizure.2010.11.014
54. He N, Min FL, Shi YW, Guo J, Liu XR, Li BM, et al. Cutaneous reactions induced by oxcarbazepine in Southern Han Chinese: incidence, features, risk factors and relation to HLA-B alleles. *Seizure.* 2012; 21(8):614-618. https://doi.org/10.1016/j.seizure.2012.06.014
55. Moon J, Kim TJ, Lim JA, Sunwoo JS, Byun JI, Lee ST, et al. HLA-B*40:02 and DRB1*04:03 are risk factors for oxcarbazepine-induced maculopapular eruption. *Epilepsia.* 2016; 57(11):1879-1886. https://doi.org/10.1111/epi.13566
56. Chen CB, Hsiao YH, Wu T, Hsih MS, Tassaneeyakul W, Jorns TP, et al. Risk and association of HLA with oxcarbazepine-induced cutaneous adverse reactions in Asians. *Neurology.* 2017; 88(1):78-86. https://doi.org/10.1212/WNL.0000000000003453
57. Fricke-Galindo I, Martínez-Juárez IE, Monroy-Jaramillo N, Jung-Cook H, Falfán-Valencia R, Ortega-Vázquez A, et al. HLA-A*02:01:01/-B*35:01:01/-C*04:01:01 haplotype associated with lamotrigine-induced maculopapular exanthema in Mexican Mestizo patients. *Pharmacogenomics.* 2014; 15(15):1881-1891. https://doi.org/10.2217/pgs.14.135
58. Moon J, Park HK, Chu K, Sunwoo JS, Byun JI, Lim JA, et al. The HLA-A*2402/Cw*0102 haplotype is associated with lamotrigine-induced maculopapular eruption in the Korean population. *Epilepsia.* 2015; 56(10):e161-167. https://doi.org/10.1111/epi.13087
59. Koomdee N, Pratoomwun J, Jantararoungtong T, Theeramoke V, Tassaneeyakul W, Klaewsongkram J, et al. Association of HLA-A and HLA-B Alleles with Lamotrigine-Induced Cutaneous Adverse Drug Reactions in the Thai Population. *Front Pharmacol.* 2017; 8:879. https://doi.org/10.3389/fphar.2017.00879
60. Küpfer A, Preisig R. Pharmacogenetics of mephenytoin: a new drug hydroxylation polymorphism in man. *Eur J Clin Pharmacol.* 1984; 26(6):753-759. https://www.ncbi.nlm.nih.gov/pubmed/6489416
61. Depondt C, Godard P, Espel RS, Da Cruz AL, Lienard P, Pandolfo M. A candidate gene study of antiepileptic drug tolerability and efficacy identifies an association of CYP2C9 variants with phenytoin toxicity. *Eur J Neurol.* 2011; 18(9):1159-1164. https://doi.org/10.1111/j.1468-1331.2011.03361.x
62. Rambeck B, Specht U, Wolf P. Pharmacokinetic interactions of the new antiepileptic drugs. *Clin Pharmacokinet.* 1996; 31(4):309-324. https://doi.org/10.2165/00003088-199631040-00006
63. Buggy Y, Layton D, Fogg C, Shakir SA. Safety profile of oxcarbazepine: results from a prescription-event monitoring study. *Epilepsia.* 2010; 51(5):818-829. https://doi.org/10.1111/j.1528-1167.2009.02489.x

64. Sun D, Yu CH, Liu ZS, He XL, Hu JS, Wu GF, et al. Association of HLA-B*1502 and *1511 allele with antiepileptic drug-induced Stevens-Johnson syndrome in central China. *J Huazhong Univ Sci Technolog Med Sci.* 2014; 34(1):146-150. https://doi.org/10.1007/s11596-014-1247-7
65. Lv YD, Min FL, Liao WP, He N, Zeng T, Ma DH, et al. The association between oxcarbazepine-induced maculopapular eruption and HLA-B alleles in a northern Han Chinese population. *BMC Neurol.* 2013; 13:75. https://doi.org/10.1186/1471-2377-13-75
66. Lin LC, Lai PC, Yang SF, Yang RC. Oxcarbazepine-induced Stevens-Johnson syndrome: a case report. *Kaohsiung J Med Sci.* 2009; 25(2):82-86. https://doi.org/10.1016/S1607-551X(09)70045-2
67. Wal P, Wal A, Pandey U, Rai AK, Bhandari A. Genetic predisposition to oxcarbazepine induced Stevens-Johnson syndrome. *Indian J Crit Care Med.* 2011; 15(3):173-175. https://doi.org/10.4103/0972-5229.84904
68. Shi YW, Min FL, Liu XR, Zan LX, Gao MM, Yu MJ, et al. Hla-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population. *Basic Clin Pharmacol Toxicol.* 2011; 109(1):42-46. https://doi.org/10.1111/j.1742-7843.2011.00681.x
69. Park HJ, Kim SR, Leem DW, Moon IJ, Koh BS, Park KH, et al. Clinical features of and genetic predisposition to drug-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a single Korean tertiary institution patients-investigating the relation between the HLA -B*4403 allele and lamotrigine. *Eur J Clin Pharmacol.* 2015; 71(1):35-41. https://doi.org/10.1007/s00228-014-1764-0
70. Park HJ, Kim YJ, Kim DH, Kim J, Park KH, Park JW, et al. HLA Allele Frequencies in 5802 Koreans: Varied Allele Types Associated with SJS/TEN According to Culprit Drugs. *Yonsei Med J.* 2016; 57(1):118-126. https://doi.org/10.3349/ymj.2016.57.1.118
71. McCormack M, Urban TJ, Shianna KV, Walley N, Pandolfo M, Depondt C, et al. Genome-wide mapping for clinically relevant predictors of lamotrigine- and phenytoin-induced hypersensitivity reactions. *Pharmacogenomics.* 2012; 13(4):399-405. https://doi.org/10.2217/pgs.11.165