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Association between the HLA-B alleles and carbamazepine-induced SJS/TEN: A meta-analysis

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ABSTRACT

Purpose: From our current understanding, the association between the human leukocyte antigen (HLA), *HLA-B**1502, and carbamazepine(CBZ)-induced Stevens-Jonson syndrome and toxic epidermal necrolysis (SJS/TEN) in the Asian population is quite clear. However the relationship between other *HLA-B* alleles and CBZ-induced severe cutaneous adverse drug reactions (SCADRs) remains unclear. We aimed to identify other non-*HLA-B*1502* alleles in patients with CBZ-induced SCADRs through a meta-analysis.

Materials and methods: A thorough literature search was performed using Embase, PubMed, Web of Knowledge and Cochrane databases. A meta-analysis was performed from their inceptions to May 31, 2016. Studies investigating the association of *HLA-B* alleles and CBZ-induced SJS/TEN were retrieved. Two reviewers independently extracted the data. Overall odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated using the RevMan 5.3 software.

Results: A total of 11 studies met the inclusion criteria, totaling 343 CBZ-induced SJS/TEN cases, 838 CBZ tolerant controls, and 978 population controls. We observed *HLA-B**1511 as a risk marker, and *HLA-B**4001 and *HLA-B**4601 as protective markers for the development of SJS/TEN in patients taking CBZ. SJS/TEN cases were found to be significantly associated with *HLA-B**1511 in both the tolerant group (OR = 17.43;95%CI = 3.12–97.41;P = 0.001) and the population-control group (OR = 11.11; 95%CI = 2.62–47.09; P = 0.001). The sensitivity analysis found that *HLA-B**5801 was a protective marker in the Southeast Asian population (OR = 0.23; 95%CI = 0.09-0.58; P = 0.002).

Conclusion: Our study demonstrated that in the Asian population, *HLA-B**4001, *HLA-B**4601, *HLA-B**5801 were strong protective factors in the development of CBZ-induced SJS/TEN whereas *HLA-B**1511 was a risk factor. While more studies may be needed in order to confirm these findings, consideration should be taken into testing Asian patients for at-risk alleles prior to CBZ therapy initiation.

1. Introduction

Carbamazepine (CBZ) is a widely prescribed medication, not only effective as a first-line antiepileptic drug, but as an effective treatment in trigeminal neuralgia and bipolar disorder (Wiffen et al., 2011). However, about 10% of patients taking CBZ will develop cutaneous adverse drug reactions (cADRs) (Marson et al., 2007). Reactions can range from mild cADRs to severe cADRs (SCADRs). Mild cADRs such as mild maculopapular exanthema (MPE) are usually self-limited, whereas severe cADRs could be life-threatening, like Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN). Although the incidence of SJS/TEN is extremely low (Chan et al., 1990), the mortality rate is up to 30% (Svensson et al., 2001). CBZ is the main causal drug that leads to the SJS/TEN (Roujeau and Stern, 1994). Although the mechanism of drug-induced SJS/TEN still remains unclear, the pathogenesis of the life-threatening cutaneous ADRs is believed to be immune mediated. The current hypothesis is that the human leukocyte antigen (*HLA)* is involved in SJS/TEN by its capacity to present CBZ to T-cells and initiate an immune response to CBZ (Chung et al., 2008). Protein molecules such as cellular drug metabolizing enzymes and T-cell receptors, as well as major histocompatibility complex (MHC), can contribute to the ensuing immunological responses and hapten formation (Yun et al., 2012). SJS/TEN is considered to be a single disease called a “bullous” cADR, while MPE is a “non-bullous” cADR. Historically, the pathogenesis of CBZ-induced SJS/TEN and MPE were thought to be different. Therefore, researchers usually discuss the relationship between SJS/TEN and MPE with gene alleles separately (Yang et al., 2015).

Many researchers have reported the association between human

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Table 1
Characteristics of studies included in the meta-analysis.

References	Population (study location)	Phenotypes studied	Case/control	Comparable groups	Patients on CBZ (n)	Patients with SJS/TEN	Drug-tolerant patients (n)	Normal controls	Method of genotyping	Reported HLA-B allele/s included in *meta*-analysis	NOS score
Hung et al. (2006)	Han Chinese (Taiwan)	SJS/TEN and HSS/MEP	**case**: CBZ was regarded as the offending drug if the onset of cADRs symptomsoccurred within the first 2 months of exposure and the symptoms resolved upon withdrawal of the drug. **Control**: patients who received CBZ for at least 3 months without evidence of adverse reactions.	Nontolerant vs. tolerant	235	60	144	N	MALDI-TOF mass spectrometry	1502, 4001	6
Tassaneeyakul et al. (2010)	Thai (Thailand)	SJS/TEN	**case**: CBZ was identified as the culprit drug if the symptoms occurred within the first 3 months of CBZ exposure and the symptoms resolved upon withdrawal of this drug. **control**: patients who had used CBZ for 6 monthswithout evidence of anycutaneous reactions were recruited as controls.	Nontolerant vs. tolerant	84	42	42	N	PCR-SBT	1502, 1521,1535,1301,1801,1802,2706,3505,3802,3909, 4001,4601,5101,5102,5502, 5601,5801	5
Kaniwa et al. (2010)	Japanese (Japan)	SJS/TEN	NR	Nontolerant vs. normal controls	28	4	N	493	PCR-SBT	1511	5
Kim et al. (2011)	Korean (Korea)	SJS/TEN and HSS/MEP	**case**:CBZ was regarded as the causative drug if the onset of the adverse reaction occurred within 2 months of exposure without another suspected high-risk drug medication in the period, and the symptoms resolved after discontinuing the drug. **control** : patients who hadreceived CBZ for at least 3 months without evidence of an adversereaction.	Nontolerant vs. tolerant **and** Nontolerant vs. normal controls	74	7	50	485	PCR locus-specific primer; PCR group-specific primer	1502,1511,5101	6
Niihara et al. (2011)	Japanese (Japan)	SJS/TEN and HSS/MEP	**Case:** patients who showed onset of cADRs within the first 3 months after starting CBZ treatment and skin rash subsided on discontinuation of treatment. **Control:** patients who did not suffer from cADRs for at least 3 months on CBZ treatment.	Nontolerant vs. tolerant	48	3	33	N	PCR-rSSO	1507,5502,1511,4002,4001,5601	6
Shi et al. (2012)	Han Chinese (southern China)	SJS/TEN	**Case:** patients who developed SJS or TEN within 8 weeks after commencing CBZ therapy, for	Nontolerant vs. tolerant	111	18	93	0	PCR-SSP; PCR-SBT	1301,1502, 1511,3802,4001,4601,5401,5601	6

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