Association between HLA–B*15:02 allele and antiepileptic drug–induced severe cutaneous reactions in Hong Kong Chinese: a population-based study

PKL Kwan *, MHL Ng, SV Lo

KEY MESSAGE

HLA-B*15:02 was strongly associated with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis.

Hong Kong Med J 2014;20(Suppl 7):S16-8
HHSRF project number: 07080381

[1] PKL Kwan *, [2] MHL Ng, [3] SV Lo

[1] *Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital*
[2] *Department of Anatomical and Cellular Pathology, The Chinese University of Hong Kong, Prince of Wales Hospital*
[3] *Division of Planning & Strategy, Hospital Authority Head Office, Hong Kong*

* Principal applicant and corresponding author: patrickkwan@cuhk.edu.hk

Introduction

The presence of HLA-B*15:02 allele greatly increases the risk of carbamazepine-induced severe cutaneous adverse drug reactions, namely Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).[1,2] It is unknown whether HLA-B*15:02 also confers increased risk of SJS/TEN induced by other anti-epileptic drugs (AEDs). HLA-B*15:02 in single cases of SJS/TEN is reported to be induced by phenytoin and lamotrigine.[1,3] This study examined the association between HLA-B*15:02 allele and SJS/TEN induced by different AEDs.

Methods

This case-control study was conducted from March 2010 to September 2011. Ethics approval was obtained from five Hospital Authority clusters. Written informed consent was obtained from each patient. Medical records of 25 male and 30 female Han Chinese patients aged 10 to 85 (mean, 44.1; standard deviation [SD], 17.1) years who presented with SJS/TEN from 1 January 1993 to 30 June 2009 within 12 weeks after commencing AEDs of carbamazepine (n=27), phenytoin (n=15), valproate (n=3), phenobarbital (n=2), lamotrigine (n=6), gabapentin (n=1), and levetiracetam (n=1) were reviewed using the Clinical Data Analysis and Reporting System.

From a DNA bank of over 1800 Han Chinese epilepsy patients, 275 controls aged 10 to 90 (mean, 44.1; SD, 16.9) years who were tolerant to AEDs after taking them for at least 3 months without developing skin rash were identified. Cases and controls were matched in age and AED prescribed in the ratio of 1:5.

DNA collected from blood and saliva samples were extracted using QIAamp DNA kit (Qiagen, Hilden, Germany) and Oragene DNA Self-Collection Kit (DNA Genotek, Ottawa, Canada), respectively. HLA-B*15:02 was detected by sequence-based typing. In brief, polymerase chain reaction was performed with primers spanning exon 2 to 3 of the HLA-B region. DNA sequencing was performed using ABI 3730xl DNA sequencer (Applied Biosystems, Foster City [CA], USA) and the resulting sequences were analysed using SBTengine (GenDx, Utrecht, The Netherlands).

Based on estimation from previous results,[1] the combined frequency of HLA-B*15:02 was assumed to be 15% in controls and 49% in cases. The sample size would have 90% power to detect a difference in frequency between cases and controls at P=0.001. Pearson Chi-square test or Fisher's exact test was used to compare the frequencies of HLA-B*15:02 between cases and controls. To account for multiple comparisons, a P value of <0.001 after Bonferroni correction was considered statistically significant.

Results

There was sample error in one case and one control, and thus only 54 cases and 274 controls were analysed. HLA-B*15:02 was associated with AED-induced SJS/TEN (63.0% of cases vs 15.3% of controls; $P=3.38 \times 10^{-14}$; odd ratios [OR]=9.39; 95% confidence interval [CI], 4.94-17.86; Table). Specifically, HLA-B*15:02 was associated with carbamazepine-induced SJS/TEN (92.3% [24/26] of cases vs 11.9% [16/135] of controls; $P=3.51 \times 10^{-18}$; OR=89.25; 95% CI, 19.25-413.83). HLA-B*15:02 was also found in 46.7% (7/15) of phenytoin-induced

TABLE. Associations between HLA-B alleles and anti-epileptic drug–induced Stevens-Johnson syndrome/toxic epidermal necrolysis

Anti-epileptic drug	HLA-B allele	No. (%) of participants		P value*	OR (95% CI)
		Cases	Controls		
All		(n=54)	(n=274)		
	B13:01	11 (20.4)	34 (12.4)	0.120	1.81 (0.85-3.84)
	B15:01	3 (5.6)	11 (4.0)	0.710	1.41 (0.38-5.22)
	B15:02	34 (63.0)	42 (15.3)	3.38×10^{-14}	9.39 (4.94-17.86)
	B15:25	1 (1.9)	4 (1.5)	1.000	1.27 (0.14-11.62)
	B35:01	2 (3.7)	8 (2.9)	0.672	1.28 (0.26-6.20)
	B38:02	8 (14.8)	31 (11.3)	0.468	1.36 (0.59-3.15)
	B40:01	6 (11.1)	66 (24.1)	0.035	0.39 (0.16-0.96)
	B46:01	8 (14.8)	69 (25.2)	0.100	0.52 (0.23-1.15)
	B51:01	3 (5.6)	9 (3.3)	0.425	1.73 (0.45-6.62)
	B51:02	4 (7.4)	8 (2.9)	0.117	2.66 (0.77-9.17)
	B54:01	1 (1.9)	10 (3.6)	1.000	0.50 (0.06-3.97)
	B55:02	1 (1.9)	14 (5.1)	0.480	0.35 (0.05-2.72)
	B56:01	2 (3.7)	7 (2.6)	0.646	1.47 (0.30-7.26)
	B58:01	2 (3.7)	51 (18.6)	0.007	0.17 (0.04-0.71)
Carbamazepine		(n=26)	(n=135)		
	B13:01	6 (23.1)	14 (10.4)	0.099	2.59 (0.89-7.54)
	B15:01	1 (3.8)	4 (3.0)	0.591	1.31 (0.14-12.22)
	B15:02	24 (92.3)	16 (11.9)	3.51×10^{-18}	89.25 (19.25-413.83)
	B15:25	0 (0)	3 (2.2)	1.000	-
	B35:01	0 (0)	3 (2.2)	1.000	-
	B38:02	2 (7.7)	15 (11.1)	1.000	0.68 (0.14-3.11)
	B40:01	1 (3.8)	42 (31.1)	0.004	0.09 (0.01-0.68)
	B46:01	3 (11.5)	32 (23.7)	0.168	0.42 (0.12-1.49)
	B51:01	2 (7.7)	2 (1.5)	0.123	5.54 (0.74-41.26)
	B51:02	0 (0)	4 (3.0)	1.000	-
	B54:01	1 (3.8)	5 (3.7)	1.000	1.04 (0.12-9.29)
	B55:02	0 (0)	8 (5.9)	0.356	-
	B56:01	0 (0)	3 (2.2)	1.000	-
	B58:01	2 (7.7)	26 (19.3)	0.256	0.35 (0.08-1.57)
Phenytoin		(n=15)	(n=74)		
	B13:01	2 (13.3)	12 (16.2)	1.000	0.80 (0.16-3.98)
	B15:01	2 (13.3)	1 (1.4)	0.072	11.23 (0.95-133.03)
	B15:02	7 (46.7)	15 (20.3)	0.047	3.44 (1.08-11.00)
	B15:25	1 (6.7)	1 (1.4)	0.310	5.21 (0.31-88.38)
	B35:01	1 (6.7)	3 (4.1)	0.529	1.69 (0.16-17.46)
	B38:02	4 (26.7)	11 (14.9)	0.271	2.08 (0.56-7.73)
	B40:01	2 (13.3)	13 (17.6)	1.000	0.72 (0.15-3.59)
	B46:01	2 (13.3)	22 (29.7)	0.338	0.364 (0.08-1.75)
	B51:01	0 (0)	3 (4.1)	1.000	-
	B51:02	2 (13.3)	3 (4.1)	0.196	3.64 (0.55-23.97)
	B54:01	0 (0)	3 (4.1)	1.000	-
	B55:02	1 (6.7)	1 (1.4)	0.310	5.21 (0.31-88.38)
	B56:01	1 (6.7)	2 (2.7)	0.429	2.57 (0.22-30.33)
	B58:01	0 (0)	16 (21.6)	0.063	-
Lamotrigine		(n=6)	(n=30)		
	B13:01	1 (16.7)	4 (13.3)	1.000	1.30 (0.12-14.21)
	B15:01	0 (0)	2 (6.7)	1.000	-
	B15:02	2 (33.3)	4 (13.3)	0.256	3.25 (0.44-23.95)
	B15:25	0 (0)	0 (0)	-	-
	B35:01	1 (16.7)	1 (3.3)	0.310	5.80 (0.31-108.60)
	B38:02	0 (0)	4 (13.3)	1.000	-
	B40:01	0 (0)	5 (16.7)	0.564	-
	B46:01	1 (16.7)	6 (20.0)	1.000	0.80 (0.08-8.19)
	B51:01	1 (16.7)	3 (10.0)	0.535	1.80 (0.15-20.99)
	B51:02	2 (33.3)	0 (0)	0.024	-
	B54:01	0 (0)	2 (6.7)	1.000	-
	B55:02	0 (0)	3 (10.0)	1.000	-
	B56:01	1 (16.7)	0 (0)	0.167	-
	B58:01	0 (0)	6 (20.0)	0.561	-

* Pearson Chi-square test or Fisher's exact test (two-sided) is used. For each drug, $P<0.004$ (0.05/14) is considered statistically significant after adjusting for multiple comparisons of 14 HLA-B types using Bonferroni correction

SJS/TEN (P=0.047; OR=3.44; 95% CI, 1.08-11.00), 33.3% (1/3) of valproate-induced SJS/TEN (P=1.000; OR=1.38; 95% CI, 0.10-19.64), and 33.3% (2/6) of lamotrigine-induced SJS/TEN (P=0.256; OR=3.25; 95% CI, 0.44-23.95). There was no HLA-B*15:02 in patients with phenobarbital-, gabapentin-, or levetiracetam-induced SJS/TEN.

There were trend associations of HLA-B*58:01 with AED-induced SJS/TEN (P=0.007; OR=0.17; 95% CI, 0.04-0.71) and HLA-B*40:01 with carbamazepine-induced SJS/TEN (P=0.004; OR=0.09; 95% CI, 0.001-0.68), but the associations were not significant after correction for multiple comparisons (Table).

Discussion

HLA-B*15:02 is associated with AED-induced SJS/TEN among Han Chinese people in Hong Kong.[1] The US Food and Drug Administration recommends HLA-B*15:02 allele testing in the ethnic groups at risk.[4] The Hospital Authority has adopted this recommendation in Hong Kong since September 2008.

In a study of a Han Chinese population from Taiwan, HLA-B*15:02 was associated with phenytoin-induced SJS/TEN (P=0.0041; OR, 5.1; 95% CI, 1.8-15.1), lamotrigine-induced SJS/TEN (P=0.1266; OR, 5.1; 95% CI, 0.8-33.8), and oxcarbazepine-induced SJS/TEN (P=0.00084; OR, 80.7; 95% CI, 3.8-1714.4).[3] In a study from Mainland China, a trend was associated with lamotrigine-induced SJS/TEN (P=0.239; OR, 10.0; 95% CI, 0.44-228.7).[5] Physicians should be cautious in prescribing aromatic AEDs (not only carbamazepine) to patients with HLA-B*15:02 allele.

In our study, HLA-B*58:01 and HLA-B*40:01 were less commonly found in patients with AED-induced SJS/TEN and with carbamazepine-induced SJS/TEN, respectively. A similar pattern for HLA-B*40:01 has been reported in a Taiwan study for carbamazepine-induced SJS/TEN (P=0.00026; OR, 0.16; 95% CI, 0.1-0.4).[1] However, there is a possibility that the lower percentage of HLA-B*40:01 found may be masked by the dominantly associated HLA-B*15:02 allele in carbamazepine-induced SJS/TEN patients.

Acknowledgements

The study was supported by the Health and Health Services Research Fund, Food and Health Bureau, Hong Kong SAR Government (#07080381). We thank collaborating neurologists in various hospitals, namely Prof Raymond TF Cheung (Queen Mary Hospital), Dr Patrick CK Li (Queen Elizabeth Hospital), Dr TH Tsoi (Pamela Youde Nethersole Eastern Hospital), and Dr BH Fung (United Christian Hospital). We wish to thank the Co-ordinating Committee (Medicine) of the Hospital Authority for endorsing the study, and Ms Edwina Shung, Senior Statistician, and her team for extracting the relevant data.

References

1. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics 2006;16:297-306.
2. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia 2007;48:1015-8.
3. Hung SI, Chung WH, Liu ZS, et al. Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. Pharmacogenomics 2010;11:349-56.
4. FDA Alert. Information for Healthcare Professionals Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). Available in URL: http://www.fda.gov:80/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm.
5. An DM, Wu XT, Hu FY, Yan B, Stefan H, Zhou D. Association study of lamotrigine-induced cutaneous adverse reactions and HLA-B*1502 in a Han Chinese population. Epilepsy Res 2010;92:226-30.