

HLA-B Alleles and Lamotrigine-Induced Cutaneous Adverse Drug Reactions in the Han Chinese Population

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Abstract: Lamotrigine (LTG) is a commonly used antiepileptic drug. However, the use of LTG is limited because of its cutaneous adverse drug reactions (cADRs) ranging from mild maculopapular eruption (MPE) to severe Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). A strong association between HLA-B*1502 and carbamazepine-induced SJS/TEN has been identified in Chinese and Thai. Although three of seven cases with HLA-B*1502 have been reported in LTG-induced SJS/TEN so far, the relationship between HLA-B*1502 and LTG-induced SJS/TEN needs further investigation. It is also unclear whether there is a specific genetic marker associated with LTG-induced MPE in Chinese. In this study, we genotyped 43 Han Chinese patients treated with LTG (14 cases with LTG-induced cADRs and 29 LTG-tolerant controls), using PCR-SSP for HLA-B*1502 testing and low-resolution genotyping, as well as sequencing for four-digit genotyping. The two cases with SJS were negative for HLA-B*1502, with B1301/1301 and 4601/5610, respectively. Combining the data with previous studies, there was no significant difference in the frequency of subjects with HLA-B*1502 between the LTG-induced SJS/TEN group and the LTG-tolerant group ($p = 0.08$, OR 4.23, 95% CI 0.94–18.97). In the MPE group, only one was positive for HLA-B*1502. There was no significant difference in the frequency of a specific HLA-B allele between the MPE group and the LTG-tolerant group either. In this study, no significant association between HLA-B*1502 and LTG-induced SJS or MPE was found. Given the small sample size and only HLA-B locus genotyping, further large-scale studies are required to explore genetic associations with LTG-induced cADRs.

Adverse drug reactions, among which cutaneous adverse drug reactions (cADRs) are most frequently encountered in the clinic, are considered as a major public health issue because of morbidity and even death. The cADRs caused by most of the antiepileptic drugs are delayed type of hypersensitivity, ranging from mild maculopapular eruption (MPE) with increasing severity to hypersensitivity syndrome (HSS), severe and life-threatening Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Antiepileptic drugs, especially drugs with aromatic structures such as carbamazepine and lamotrigine (LTG), are among the most common causes of severe cADRs [1–3]. Therefore, the prevention of these cADRs is an important goal for anticonvulsant therapy.

Recent pharmacogenetic studies have identified a striking genetic association between HLA-B*1502 and carbamazepine-induced SJS and TEN in Han Chinese and Thai populations [4–6], but not in Caucasians and Japanese [6,7]. In addition, a strong association between HLA-B*5801 and allopurinol-induced HSS and SJS/TEN has been reported in Han Chinese and European populations [8,9]. Till now, three

of seven cases with LTG-induced SJS/TEN have been reported to be positive for HLA-B*1502 in Han Chinese patients [10,11], but no single major HLA-related genetic risk factor has been identified for LTG-induced SJS/TEN or HSS in patients of European origin [12]. Whether there is a genetic marker for LTG-induced SJS/TEN thus needs further investigation. On the other hand, an association between carbamazepine-induced MPE and HLA-B*1502 was not found in these case series studies in Chinese and Thai [4,13]. The relationship between LTG-induced MPE and HLA-B*1502 or any of other HLA-B alleles has not been reported. In this study, we aimed to look for an association between LTG-induced cADRs and all HLA-B alleles in the Han Chinese population.

Materials and Methods

Subjects. A total of 14 epileptic patients with LTG-induced cADRs (two cases with SJS and 12 cases with MPE) were recruited for this study from 2008 to 2010 in the epilepsy centre of the 2nd Affiliated Hospital of Guangzhou Medical University. All patients developed cADRs within 8 weeks after commencing LTG and for which no other causes were found. SJS was defined according to Roujeau's diagnostic criteria [14] with skin detachment of 10% or less of body surface area. Conjunctivae and oral mucosa were affected in both cases with SJS. MPE was denoted to those with erythematous exanthem without blistering or pustulation, which spontaneously resolved within 1–2 weeks after discontinuation of LTG. Except for three patients with MPE who had fever, the other nine did not have systemic manifestations. After 3 months of LTG treatment, twenty-nine

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epileptic patients without cADRs were recruited as tolerant controls. All individuals enrolled were unrelated ethnic Han Chinese, and most of them lived in the Guangdong province. None of the four biological grandparents were from other races. Additionally, we set up another normal control group. The allele frequencies of normal populations came from the Southern Han Chinese [15] and the Hong Kong Chinese population (<http://www.allelefrequencies.net/default.asp>). The study was approved by the institutional review board of the hospital, and informed consent was obtained from all participants.

HLA-B genotyping Genomic DNA was extracted from blood samples using QIAamp blood mini kit (Qiagen, Hilden, Germany). HLA-B*1502 testing was performed by polymerase chain reaction with sequence-specific primers (PCR-SSP) specifically for HLA-B*1502 [16]. In brief, six separated PCRs (including four HLA-B*1502-specific PCRs and two internal control PCRs) were performed in a total of 25 µl buffer containing 30–50 ng DNA, 200 µM dNTPs, 1.25 U *Taq* polymerase (TaKaRa, Japan) and 1 µM primers. The procedure of PCR was as follows: 96°C, 60 sec.; 4 cycles of 96°C, 30 sec., 62°C, 45 sec., 72°C, 45 sec.; 21 cycles of 96°C, 10 sec., 58°C, 45 sec., 72°C, 45 sec.; and nine cycles of 96°C, 10 sec., 55°C, 50 sec., 72°C, 1 min. and 30 sec. PCR products were analysed on a 2.0% agarose gel. Presence of all fragments denotes HLA-B*1502. Further low-resolution genotyping was employed to genotyped HLA-B alleles using Micro SSP HLA Class IB Locus Specific Tray (One Lambda, Canoga Park, CA, USA) according to the manufacturer's instructions. After migration of PCR products on 2% agarose gels, HLA-B allele types were determined with the aid of the GenoVision Helmborg-SCORE software (Qiagen Inc., Valencia, CA, USA). To obtain four-digit allele types, samples were sequenced on an ABI 3730 automated sequencer (PE Applied Biosystems, Foster City, CA, USA). The forward and reverse sequence primers were Bin1-TAF (5'-TGGCGGGGCGCAGGACCTGA-3') or Bin1-CGF (5'-TCGGGGGCGCAGGACCCGG-3') and Bin3-R (5'-CGGAGGCCATCCCCGCGACCTAT-3'). All sequence results were carried out by BLASTN (<http://www.ncbi.nlm.nih.gov/BLAST/>) and analysed by the software vector NTI 6.0 (Informax Inc., Gaithersburg, MD, USA).

Statistical analysis. Statistical analysis was performed using SPSS version 11.5 (SPSS, Chicago, IL, USA). Independent *t*-test was used to determine the difference in mean age and dosage between the cADRs and the tolerant group. A 2-by-2 χ^2 test for each allele fre-

quency between patients and controls was performed. The *p*-value from continuity correction ($n \geq 40$ but $1 \leq T \leq 5$) or Fisher's exact test ($n < 40$ or $T < 1$), as well as estimated odds ratios (OR) and 95% exact confidence interval (CI), was obtained. To reduce bias in estimating the odds ratio whenever a zero-count cell was encountered, 0.5 was added to all cells in a 2 × 2 table [17]. *p*-Value of <0.05 (two-sided) was considered statistically significant.

Results

The age, sex, clinical manifestations and HLA-B allele distributions of all subjects are summarized in table 1 (SJS and MPE cases) and table S1 (tolerant controls). There was no significant difference between the cADRs group and the tolerant group regarding mean age (21.79 ± 24.37 years *versus* 18.9 ± 9.67 years, $p = 0.68$), sex ratio (female/total, 7/14 *versus* 12/29, $p = 0.59$), initial dose of LTG (25.00 ± 25.24 mg/day *versus* 12.44 ± 5.5 mg/day, $p = 0.09$) or concurrent use of valproate (VPA, 2/14 *versus* 12/29, $p = 0.095$). Among those with MPE, three patients were taking other antiepileptic drugs when LTG was started, but they recovered only after discontinuation of LTG. Patient P6 took LTG after having used VPA for 1 month; patient P24 took LTG when using topiramate for 58 days; patient P44 had taken carbamazepine, topiramate and VPA for more than 6 months when LTG was started. The mean duration of drug exposure was 17.64 ± 10.62 days before cADRs occurred.

We obtained the results of HLA-B*1502-specific testing and HLA-B low-resolution genotyping in all 43 individuals and obtained the four-digit genotype results in 41 subjects by sequencing (two samples were no longer available). The results of four-digit genotype were matched with low-resolution genotyping in 39 subjects (tables 1 and S1), except in two tolerant controls (CN5 and CN20 table S1).

Both cases with SJS were negative for HLA-B*1502 with genotypes B*1301/1301 and B*4601/5610, respectively

Table 1.

Clinical characteristics and HLA-B genotyping of the patients with LTG-induced cADRs.

Patient	Sex	Age ¹ (years)	Phenotype	Initial dose (mg/day)	Final dose (mg/day)	Latency to cADRs (days)	Concurrent drugs	HLA-B*1502	HLA-B diplotype	Four-digit allele
P14	M	14	SJS	12.5	50	22	None	–	B13/B13	1301/1301
P63	F	24	SJS	6.25	12.5	17	None	–	B46/56	4601/5610
P6	F	17	MPE	12.5	50	28	VPA	+	B62/46	1502/4601
P24	M	3	MPE	6.25	12.5	30	TPM	–	B60/60	4001/4001
P39	M	21	MPE	50	50	3	None	–	B38/44	NA
P44	M	4	MPE	25	50	14	CBZ, TPM, VPA	–	B39/48	3901/4801
P47	F	2	MPE	6.25	25	33	None	–	B54/58	5401/5801
P50	F	74	MPE	12.5	25	13	None	–	B46/58	4601/5801
P66	F	13	MPE	6.25	37.5	32	None	–	B60/81	4001/8101
P75	M	79	MPE	25	75	18	None	–	B60/55	4001/5502
P77	F	7	MPE	25	25	2	None	–	B60/60	4001/4001
P82	F	24	MPE	25	200	18	None	–	B46/46	4601/4601
P84	M	17	MPE	100	150	15	None	–	B13/46	1301/4601
P85	M	6	MPE	37.5	37.5	2	None	–	B13/13	1302/1302

¹Age at the development of cADRs.

cADRs, cutaneous adverse drug reactions; CBZ, carbamazepine; LTG, lamotrigine; MPE, mild maculopapular eruption; NA, data not available because of insufficient DNA of the sample; SJS, Stevens–Johnson syndrome; TPM, topiramate; VPA, valproate; +, positive; –, negative.

(table 1). When we pooled the data (0/2) with those from the Hong Kong (1/1) and Taiwan (2/6) studies, there was no significant difference in the frequency of HLA-B*1502 allele between the LTG-induced SJS/TEN group and the LTG-tolerant controls (3/9 versus 11/123, $p = 0.08$, OR 4.23, 95% CI 0.94–18.97). Similarly, there was no significant difference in the frequency of HLA-B*1502 allele between the LTG-induced MPE (4.5%, 1/22) and the tolerant controls (7.1%, 4/56; $p = 1.00$, OR 0.62, 95% CI 0.07–5.87) and the normal control group (7.3%; $p = 1.00$, OR 0.60, 95% CI 0.08–4.56). There was no difference in the two control groups either ($p = 1.00$, OR 0.96, 95% CI 0.33–2.81).

When comparing the frequency of each four-digit allele of HLA-B between MPE and tolerant controls, and between MPE and normal population controls, no significant difference was found (p -values >0.05 , Table 2). It was noted that one case with MPE had a very rare allele, HLA-B*8101.

Discussion

In the present study, HLA-B*1502 was absent in the two LTG-induced SJS cases. Previous studies have reported one LTG-induced TEN case, and two of six LTG-induced SJS cases were positive for HLA-B*1502 in the Hong Kong and Taiwan studies, respectively [10,11]. Given the small sample size in these studies, we pooled our data with those from the Hong Kong and Taiwan studies. No significant association between HLA-B*1502 and LTG-induced SJS was

found. In contrast, a strong association between HLA-B*1502 and carbamazepine-induced SJS/TEN in the Han Chinese has previously been demonstrated [5,10,13]. The present study suggests that LTG-induced SJS/TEN may be different from carbamazepine-induced SJS/TEN in association with HLA-B*1502, at least not as strong as that of carbamazepine-induced SJS/TEN in the Han population. In other words, it is indicated that the association between HLA-B*1502 and SJS/TEN is drug specific, although LTG shares a similar chemical structure with carbamazepine. From another point of view, it is noted that the association between HLA-B*1502 and carbamazepine-induced SJS/TEN lacked in Japanese and European populations [6,7], which is possibly because of the low frequency of HLA-B*1502 in these populations (0.1% in the Japanese population and 0% in the German and French populations, data from [18]). Additionally, HLA-B*5801 has been reported to be associated with allopurinol-induced SJS in the Han Chinese and European populations [8,9], which may be caused by the similar high frequency of this allele in these populations (2.9–10.0% in the Han population and 4.5% in the French population, data from <http://www.allele-frequencies.net>). These data suggest that genetic associations regarding SJS/TEN are not only drug specific but also ethnicity specific.

Previous studies have shown that HLA-B*5801 and B*38 were weakly associated with LTG-induced SJS in European populations [8,12]. Such an association has not been found in the Han Chinese cases so far; further studies with large

Table 2.

Association of four-digit HLA-B alleles with LTG-induced MPE.

HLA-B Allele	Frequency (%)		MPE (2n = 22)	MPE cases versus LTG-tolerant controls		MPE cases versus population controls	
	LTG-tolerant controls (2n = 56)	Population controls (2n = 528)		OR (95% CI)	p value	OR (95% CI)	p value
0705	1/56 (1.8)	9/528 (1.7) ¹	0/22 (0.0)	1.23 (0.11–14.09)	1.00	2.26 (0.28–18.42)	0.39
1301	9/56 (16.1)	36/528 (6.8) ¹	1/22 (4.5)	0.25 (0.030–2.091)	0.32	0.65 (0.09–4.98)	1.00
1302	2/56 (3.6)	11/528 (2.1) ¹	2/22 (9.1)	2.70 (0.36–20.48)	0.67	4.70 (0.98–22.62)	0.09
1502	4/56 (7.1)	39/528 (7.3) ¹	1/22 (4.5)	0.62 (0.07–5.87)	1.00	0.60 (0.08–4.56)	0.93
1503	2/56 (3.6)	1/528 (0.2) ¹	0/22 (0.0)	0.80 (0.08–8.07)	1.00	11.48 (1.00–131.23)	0.13
1519	1/56 (1.8)	0/569 (0.0) ²	0/22 (0.0)	1.22 (0.11–14.09)	1.00	24.78 (1.50–408.76)	0.08
1527	2/56 (3.6)	1/528 (0.2) ¹	0/22 (0.0)	0.80 (0.08–8.07)	1.00	11.48 (1.00–131.23)	0.13
3901	1/56 (1.8)	7/528 (1.3) ¹	1/22 (4.5)	2.62 (0.16–43.81)	0.49	3.54 (0.42–30.13)	0.28
4001	10/56 (17.9)	76/528 (14.4) ¹	6/22 (27.3)	1.73 (0.54–5.51)	0.54	2.23 (0.85–5.88)	0.18
4403	1/56 (1.8)	9/528 (1.7) ¹	0/22 (0.0)	1.22 (0.11–14.09)	1.00	2.26 (0.28–18.42)	0.39
4408	1/56 (1.8)	0/569 (0.0) ²	0/22 (0.0)	1.22 (0.11–14.09)	1.00	24.78 (1.50–408.76)	0.08
4601	12/56 (21.4)	63/528 (11.9) ¹	5/22 (22.7)	1.08 (0.33–3.52)	1.00	2.17 (0.77–6.09)	0.24
4801	1/56 (1.8)	11/528 (2.1) ¹	1/22 (4.5)	2.62 (0.16–43.81)	0.49	2.24 (0.28–18.15)	0.39
5401	1/56 (1.8)	13/528 (2.5) ¹	1/22 (4.5)	2.62 (0.16–43.81)	0.49	1.89 (0.24–15.10)	0.44
5417	1/56 (1.8)	NR	0/22 (0.0)	1.22 (0.11–14.09)	1.00		
5501	4/56 (7.1)	0/569 (0.0) ²	0/22 (0.0)	0.46 (0.05–4.17)	0.81	24.78 (1.50–408.76)	0.08
5502	0/56 (0.0)	12/569 (2.2) ²	1/22 (4.5)	5.18 (0.45–60.07)	0.20	2.21 (0.27–17.80)	0.39
5801	3/56 (5.4)	47/528 (8.9) ¹	2/22 (9.1)	1.77 (0.28–11.37)	0.92	1.02 (0.23–4.51)	1.00
8101	0/56 (0.0)	1/569 (0.2) ²	1/22 (4.5)	5.18 (0.45–60.07)	0.20	27.05 (1.64–447.38)	0.07

¹From a southern Han Chinese population of 264 persons (Trachtenberg *et al.*, 2007).

²From a Hong Kong Chinese population of 569 persons (<http://www.allele-frequencies.net>). The frequency of these alleles has not been reported by Trachtenberg.

LTG, lamotrigine; MPE, mild maculopapular eruption; NR, not reported by superscript 1 and 2.

samples are needed to confirm this. Besides HLA-B, another marginal association with LTG-induced SJS/TEN was observed for the alleles HLA-Cw*0718, DQB1*0609, A*6801 and DQB1*1301 in cases of European ancestry [12]. This suggests that there may be no single HLA allele that is associated with LTG-induced SJS/TEN. Limited by only HLA-B locus genotyping in this study, other HLA alleles or genetic factors that may contribute to LTG-induced SJS/TEN should be investigated further.

Clinically, MPE is more common than HSS or SJS/TEN. The rate of LTG-induced MPE is higher than the overall incidence rate of antiepileptic drug-induced MPE (4.8% versus 2.8%) [19,20]. Thus, it would be of practical significance to find genetic markers for LTG-induced MPE. We did not find a significant association between HLA-B*1502 and LTG-induced MPE in the Han Chinese in this study, similar to carbamazepine-induced MPE [13]. Further, we did not find a significant association between any of the other HLA-B alleles and LTG-induced MPE. A major limitation of these similar studies was the sample size available for the analysis. So, we performed a post hoc power analysis as in the previous study [12]. On the condition that the prevalence of LTG-induced MPE was 4.8% [19] and a type 1 error rate (α) set at 0.05, the present study had approximately 80% statistical power to detect an effect size of 21 for alleles with frequency of 1%. Therefore, this study had approximately 80% power to detect an observed HLA-B allele with a frequency of 1%. Then, apart from the alleles with a frequency <1%, the other observed alleles with a frequency more than 1%, such as HLA-B*1502, had approximately 80% or more statistical power to suggest that there is no association between the allele and LTG-induced MPE. It was interesting to observe that one LTG-induced MPE case carried HLA-B*8101 in the present study. A British study of European patients showed an association between carbamazepine-induced HSS and an ancestral haplotype of HLA-B8.1 that consists of HLA-B*8101 and other alleles [6]. As mentioned above, for alleles with frequencies <1%, there was low power to detect any effect size <21. HLA-B*8101 was present in a frequency as low as 0.2% in the Han population; thus, the relationship between the allele and LTG-induced MPE warrants studies with large samples. On the other hand, carbamazepine-induced MPE had been reported to be associated with HLA-A*3101 in a Han Chinese study [13]. Therefore, other regions of the genome should be screened for genetic associations with LTG-induced MPE.

Other factors, such as age, gender, higher starting dose, rapid titration schedule and concomitant use of VPA, have been reported as risk factors for LTG-induced adverse events [21,22]. In the present study, we did not find any significant difference in mean age, sex ratio and initial dose between the cADRs group and the tolerant group. A study from Taiwan showed that tolerant patients received higher or comparable dosage than the cADRs group [11]. These data suggest that the major factors for the development of LTG-induced cADRs need to be investigated further.

In the present study, no significant association between HLA-B*1502 and LTG-induced SJS/TEN or MPE was found in the Han Chinese population. Limited by the small sample size and only HLA-B locus genotyping in this study, it is worthwhile to carry out a meta-analysis on large multi-centre data from various regions to determine the exact association between HLA-B*1502 and LTG-induced cADRs, as well as search for other genetic associations regarding LTG-induced cADRs.

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Supporting Information

Additional Supporting information may be found in the online version of this article:

Table S1. Clinical characteristics and HLA-B genotyping of LTG-tolerant controls.

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