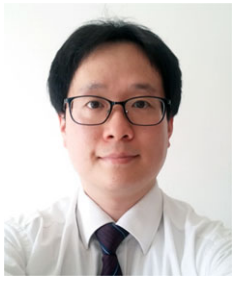
BRIEF COMMUNICATION

The HLA-A*2402/Cw*0102 haplotype is associated with lamotrigine-induced maculopapular eruption in the Korean population

*†[1]Jangsup Moon, ‡[1]Han-Ki Park, *†Kon Chu, *†Jun-Sang Sunwoo, *†Jung-Ick Byun, *†Jung-Ah Lim, *†Tae-Joon Kim, §Jung-Won Shin, *†Soon-Tae Lee, *†Keun-Hwa Jung, *†Ki-Young Jung, *†Daejong Jeon, ¶Dong Wook Kim, #Kyung-Sang Yu, #In-Jin Jang, ‡Hye-Ryun Kang, ‡Heung-Woo Park, and *†Sang Kun Lee

Epilepsia, 56(10):e161–e167, 2015
doi: 10.1111/epi.13087



Jangsup Moon is a research fellow at Seoul National University Hospital.

Han-Ki Park is an allergist, who is interested in bioinformatics and extracellular vesicles.

Summary

The use of lamotrigine (LTG) can be limited by the occurrence of cutaneous adverse drug reactions (cADRs) that range from maculopapular eruption (MPE) to the more severe Stevens-Johnson syndrome and toxic epidermal necrolysis. A few human leukocyte antigen (HLA)–related genetic risk factors for carbamazepine-induced cADR have been identified. However, the HLA-related genetic risk factors associated with LTG-induced cADR are not yet well known. We performed HLA genotyping in 50 Korean patients with epilepsy, including 21 patients presenting LTG-induced MPE and 29 LTG-tolerant patients. A significant association between the HLA-A*2402 allele and LTG-induced MPE was identified, in comparison with the LTG-tolerant group (odds ratio [OR] 4.09, p = 0.025) and the general Korean population (OR 3.949, p = 0.005). The frequencies of the Cw*0102 or Cw*0702 alleles were significantly higher in the LTG-MPE group than in the Korean population, whereas the frequency of the A*3303 allele was lower. The coexistence of the A*2402 and Cw*0102 alleles was significantly associated with the LTG-MPE group when compared to the LTG-tolerant group (OR 7.88, p = 0.007). In addition, the Cw*0701 allele was more frequent in the LTG-tolerant group than in the Korean population. These findings suggest the presence of HLA-related genetic risk factors for LTG-induced MPE in the Korean population.

KEY WORDS: Lamotrigine, Rash, Maculopapular eruption, Cutaneous adverse reaction, HLA.

Lamotrigine (LTG) is a commonly used broad-spectrum antiepileptic drug (AED)—which is also widely used as an effective mood stabilizer—that does not cause any cognitive adverse effect. Therefore, it can be prescribed in elderly patients and achieves an excellent retention rate due to good drug compliance.[1] However, the most concerning disadvantage of LTG is the possibility of cutaneous adverse drug reaction (cADR). The incidence of serious rashes requiring

hospitalization ranges between 0.1% and 1%, whereas non-serious rashes occur in approximately 10% of the patients who receive LTG.[2]

Pharmacogenomics studies have identified a striking association between the human leukocyte antigen (HLA)-B*1502 allele and the carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) in the Han Chinese population.[3] However, no major HLA-related genetic risk factors for the LTG-induced cADRs have been identified so far. Only a limited number of studies enrolling a small number of patients have suggested a few risk factors.[4] In the current study we aimed to identify HLA-related genetic risk factors in Korean patients with LTG-induced maculopapular eruption (MPE).

Methods

Patients

Among the patients with epilepsy who visited the Seoul National University Hospital, those who experienced MPE after LTG administration were enrolled in our study to compose the LTG-MPE group. Upon the clinical identification of MPE, LTG was immediately discontinued to prevent the patients from experiencing severe cutaneous adverse reactions (SCARs), such as SJS/TEN. Patients were enrolled (1) when MPE occurred within 6 weeks after the last dose escalation of LTG or when LTG was the only offending drug exposed to the patient, and (2) when the rash was resolved after discontinuation of LTG. Patients with following conditions were excluded: (1) incomplete clinical data, or (2) difficulty in identifying the causative drug. As control groups, we used both an LTG-tolerant group and the general Korean population.[5] The LTG-tolerant group was composed of patients who had received ≥300 mg/day of LTG and had a documented medical history of LTG serum levels >10 μg/ml without any cADR during a minimum of 1 year of LTG treatment. The study was approved by the institutional review board of the Seoul National University Hospital and written informed consent was obtained from every patient.

HLA genotyping

Genomic DNA was extracted from the peripheral blood of every patient from the LTG-MPE and LTG-tolerant groups, and HLA genotyping was performed. The genotypes of the *HLA-A, HLA-B, HLA-C, HLA-DRB1*, and *HLA-DQB1* genes of each subject were determined at the allele level using direct DNA sequence analysis following the established protocols (Biowithus, Seoul, Korea).[6] The previously reported HLA frequencies in the Korean population were used for the general population control group values.[5]

Statistical analyses

Fisher's exact test was used to assess the differences between the HLA genotype frequencies among the LTG-MPE and control groups. Odds ratio (OR) and 95% confidence interval (CI) values were obtained, and a p-value < 0.05 (two-tailed) was considered statistically significant. The statistical analyses were conducted using the SPSS software version 22.0 (SPSS, Chicago, IL, U.S.A.).

Results

A total of 21 patients were recruited in the LTG-MPE group, and 29 patients were included in the LTG-tolerant group. The clinical characteristics and HLA genotypes of the enrolled patients are shown in Table 1. The genotype frequency of the HLA-A*2402 allele was significantly higher in the LTG-MPE group compared with both the LTG-tolerant group ($p = 0.025$, OR 4.09, 95% CI 1.22–13.69) and the general Korean population ($p = 0.005$, OR 3.949, 95% CI 1.51–13.36). In the LTG-MPE group, the frequencies of the Cw*0102 or the Cw*0702 alleles were significantly higher and the frequency of the A*3303 allele was lower than in the Korean population, whereas the differences were not statistically significant compared with the LTG-tolerant group. Concomitant A*2402 and Cw*0102 alleles were significantly more frequent in the LTG-MPE group than in the LTG-tolerant group ($p = 0.007$, OR 7.88, 95% CI 1.81–34.28; Table 2). On the other hand, the frequencies of the Cw*0701 or the Cw*0304 alleles were higher in the LTG-tolerant group than in the Korean population ($p = 0.003$, OR 18.538, 95% CI 3.57–96.36 and $p = 0.001$, OR 4.169, 95 CI 1.88–9.24, respectively). None of the patients in the LTG-MPE group had Cw*0701, which is encouraging to interpret this as a protective allele; however, Cw*0304 was not significantly lower in the LTG-MPE group when compared to the LTG-tolerant group (Table 2). The HLA-DRB1*1101 genotype frequency was

Accepted June 19, 2015; Early View publication August 17, 2015.

*Department of Neurology, Laboratory for Neurotherapeutics, Comprehensive Epilepsy Center, Biomedical Research Institute, Seoul National University Hospital, Seoul, Korea; †Program in Neuroscience, Seoul National University College of Medicine, Seoul, Korea; ‡Department of Internal Medicine, Institute of Allergy and Clinical Immunology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea; §Department of Neurology, CHA Bundang Medical Center, CHA University, Seoungnam, Korea; ¶Department of Neurology, Konkuk University College of Medicine, Seoul, Korea; and #Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine and Hospital, Seoul, Korea

Address correspondence to Kon Chu and Sang Kun Lee, Department of Neurology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea. E-mails: stemcell.snu@gmail.com and sangkun2923@gmail.com

[1]These authors contributed equally to this work.

Table 1. Clinical characteristics and HLA genotypes of the patients

ID	Gender	Age	Manifestation	Maximum dose (mg/day)	Latency (initial day)[a]	Latency (maximum day)[b]	Documented LTG level (μg/ml)	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1
LTG-induced MPE												
1	F	54	MPE + eosinophilia	25	17	17	(−)	2402/2601	4002/5401	0102/0303	0803/1101	0301/0601
2	F	28	MPE + fever + cytopenia	50	11	2	(−)	0201/2402	1511/5901	0102/0303	0405/0901	0303/0401
3	F	28	MPE + fever	50	14	14	(−)	0207/2402	0702/4601	0102/0702	0101/0803	0501/0601
4	F	22	MPE + fever + eosinophilia	200	36	1	(−)	2402/2602	1501/4601	0102/0303	0405/0901	0303/0401
5	F	30	MPE	25	5	5	(−)	2402/2601	2705/5201	0102/1202	0101/1502	0501/0601
6	F	17	MPE	25	13	13	(−)	2402/2402	0702/0702	0702/0702	0101/0405	0401/0501
7	M	25	MPE	25	35	35	(−)	2402/2602	0702/5401	0102/0702	0101/0405	0401/0501
8	F	77	MPE	37.5	4	4	(−)	0201/1101	5101/6701	0702/1502	0403/1602	0302/0502
9	M	28	MPE	50	5	5	(−)	0207/3303	4601/5801	0102/0302	0803/1302	0601/0609
10	M	21	MPE	50	11	11	(−)	1101/2402	1501/4001	0304/0401	0406/1101	0301/0302
11	F	21	MPE	50	11	4	(−)	0201/2901	1511/5102	0303/1502	1454/1501	0502/0503
12	F	48	MPE	100	20	7	(−)	1101/1101	2705/4001	0202/0304	0403/1101	0301/0302
13	F	22	MPE	100	27	13	(−)	1101/2402	1501/2705	0102/0401	0101/0406	0302/0501
14	F	18	MPE	100	28	28	(−)	2402/2402	1301/5401	0304/0803	0405/1202	0301/0401
15	F	49	MPE	100	35	7	(−)	0201/2402	4006/4601	0102/0801	0803/1201	0301/0601
16	F	22	MPE	100	40	13	(−)	2402/3101	3901/5401	0102/0702	0403/0405	0302/0401
17	F	75	MPE	100	40	15	(−)	2402/2601	1501/5801	0302/0303	0901/1201	0301/0303
18	F	33	MPE	100	45	16	(−)	0203/2402	3802/5401	0102/0702	0405/1502	0401/0501
19	F	21	MPE	100	63	42	(−)	0201/2402	3901/5101	0702/1402	0809/1101	0301/0402
20	M	12	MPE	100	117	82	(−)	1101/2602	1501/1501	0102/0303	0803/1406	0301/0601
21	M	15	MPE	200	68	38	(−)	0201/3201	4006/4402	0501/0801	0901/1201	0302/0303
LTG-tolerant												
22	F	36	(−)	700	N/A	N/A	17.73	0207/1101	4601/5901	0102/0102	0405/0803	0401/0601
23	F	22	(−)	500	N/A	N/A	15.6	0101/2601	3701/4002	0304/0602	1201/1501	0301/0602
24	M	26	(−)	500	N/A	N/A	13.05	2601/3303	4403/5101	0304/1403	1302/1454	0502/0604
25	F	39	(−)	500	N/A	N/A	12.95	1101/2402	4001/5101	0304/1402	1101/1405	0301/0303
26	M	38	(−)	400	N/A	N/A	15.64	0207/2601	3901/4403	0701/0702	0803/0803	0601/0601
27	F	29	(−)	400	N/A	N/A	14.52	2602/3101	3501/3901	0303/0702	0403/0403	0302/0302
28	F	22	(−)	400	N/A	N/A	12.58	2402/3303	1518/5801	0302/0801	0803/1101	0301/0601
29	F	25	(−)	400	N/A	N/A	12.44	0201/2402	1501/5101	0102/1402	0803/1405	0503/0601
30	M	29	(−)	400	N/A	N/A	11.73	0206/1101	1501/4006	0303/0801	1101/1501	0301/0602
31	M	43	(−)	400	N/A	N/A	11.64	1101/3101	1501/4601	0102/0102	0901/1201	0301/0303
32	F	42	(−)	400	N/A	N/A	10.44	0207/2602	1301/1501	0303/0304	1201/1202	0301/0301
33	M	32	(−)	400	N/A	N/A	10.24	2402/3303	4403/5401	0102/0701	0405/0701	0202/0401
34	F	20	(−)	350	N/A	N/A	15.4	0201/0206	1518/5101	0704/1402	0802/0802	0302/0402
35	M	26	(−)	350	N/A	N/A	12.67	0201/2601	5101/5401	0102/1402	0405/1454	0401/0502
36	M	19	(−)	350	N/A	N/A	10.83	2402/2601	4001/4002	0304/0304	0101/1101	0301/0501
37	F	18	(−)	300	N/A	N/A	16.68	0201/2402	3802/5201	0702/1202	1454/1502	0401/0601
38	F	24	(−)	300	N/A	N/A	15.6	1101/2402	4006/5101	0102/1402	0901/1101	0301/0303
39	M	25	(−)	300	N/A	N/A	12.1	0101/3303	3701/5801	0302/0602	1001/1302	0501/0609

Continued

Epilepsia, 56(10):e161–e167, 2015
doi: 10.1111/epi.13087

Table 1. Continued.

ID	Gender	Age	Manifestation	Maximum dose (mg/day)	Latency (initial day)[a]	Latency (maximum day)[b]	Documented LTG level (μg/ml)	HLA-A	HLA-B	HLA-C	HLA-DRB1	HLA-DQB1
40	M	28	(−)	300	N/A	N/A	11.85	2402/2402	1301/1501	0304/0401	0803/1202	0301/0601
41	M	38	(−)	300	N/A	N/A	11.57	0201/3303	1501/5801	0302/0801	0301/1501	0201/0602
42	M	23	(−)	300	N/A	N/A	11.21	2402/3002	1302/4002	0304/0602	0401/0701	0202/0301
43	M	19	(−)	300	N/A	N/A	11.13	2402/3303	0702/4001	0304/0702	0101/1454	0501/0503
44	M	35	(−)	300	N/A	N/A	10.96	0201/0201	1501/4002	0102/0304	0901/1301	0303/0603
45	F	20	(−)	300	N/A	N/A	10.8	2402/2402	1507/4002	0303/0304	0403/1201	0302/0303
46	F	40	(−)	300	N/A	N/A	10.66	1101/3303	4001/4403	0304/0701	0701/1202	0202/0301
47	F	39	(−)	300	N/A	N/A	10.64	0101/0201	3501/5101	0401/1402	0101/0901	0303/0501
48	M	47	(−)	300	N/A	N/A	10.59	3001/3303	1302/5801	0302/0602	0701/1302	0202/0609
49	M	43	(−)	300	N/A	N/A	10.2	0206/0207	3501/4601	0102/0303	0901/1101	0301/0303
50	M	43	(−)	300	N/A	N/A	10.03	1101/2602	1501/5401	0102/0401	0405/0406	0302/0401

F, female; M, male; MPE, maculopapular eruption; LTG, lamotrigine; N/A, not applicable.
[a]Latency between initial exposure to LTG and onset of MPE.
[b]Latency between last dose escalation of LTG and onset of MPE.

also increased in the LTG-tolerant group compared with the Korean population; however, the number of DRB*1101-positive patients was similarly distributed in both the LTG-MPE and the LTG-tolerant groups.

Discussion

In the present study, we identified significant associations between LTG-induced MPE and the HLA-A*2402, HLA-Cw*0102, and HLA-Cw*0702 alleles, whereas the HLA-A*3303 allele was identified as a protective allele. The coexistence of the HLA-A*2402 and the Cw*0102 alleles (A*2402/Cw*0102 haplotype) was identified as the strongest risk factor for LTG-induced MPE. In addition, the HLA-Cw*0701 allele was associated with a tolerance to hypersensitivity reactions after high-dose LTG treatment. Our results provide useful information for the clinical practitioners concerning LTG administration, especially in patients from the Korean population.

The best known genetic risk factor for an AED-related cADR is the association between the HLA-B*1502 allele and CBZ-induced SJS/TEN in the Han Chinese population.[3] However, subsequent studies have identified the ethnic differences of the HLA genotype-related risk factors, even in other Asian populations.[7] Indeed, instead of HLA-B*1502, the HLA-A*1511 and the A*3101 alleles have been identified as the risk factors for CBZ-induced SJS/TEN in the Japanese[8,9] and Korean populations.[6] In addition, later studies have revealed that the HLA genotype–related associations were different for MPE than for SJS/TEN. In Han Chinese, the HLA-B*1502 allele was not associated with CBZ-induced MPE in most of the studies. Instead, the HLA-A*3101 allele was suggested as a risk factor for CBZ-induced MPE in this ethnic group.[7] These results suggest that the mechanism underlying drug-induced MPE might differ from that of the SCARs, such as SJS/TEN.

So far, no single major HLA-related genetic risk factor for LTG-induced cADRs has been established.[4] Several studies in the Han Chinese population have failed to demonstrate any significant association between the HLA-B*1502 allele and LTG-induced SJS/TEN or MPE.[4] However, associations between the HLA-A*3001 and B*1302 alleles and LTG-induced MPE have been reported in Han Chinese.[10] Among other population groups, the HLA-B*5801, A*6801, Cw*0718, DQB1*0609, and DRB1*1301 alleles were reported to be weakly associated with LTG-induced cADR in patients of European origin,[11] and the HLA-A*020101/B*350101/C040101 haplotype has been suggested as a biomarker for LTG-induced MPE in Mexican Mestizo patients.[12]

In this study, we identified three risk factor alleles (A*2402, Cw*0102, and Cw*0702) and two protective alleles (A*3303 and Cw*0701) for LTG-induced MPE. Among them, the risk of LTG-induced MPE was most prominently increased in patients carrying the HLA-A*2402 allele.

Table 2. Associations between four-digit HLA alleles and LTG-induced MPE

HLA allele	Frequency			MPE versus LTG-tolerant		MPE versus general population		LTG-tolerant versus general population	
	MPE (%)	LTG-tolerant (%)	General population (%)	OR	p-Value	OR	p-Value	OR	p-Value
A*2402	15/21 (71.4)	12/29 (41.4)	188/485 (38.8)	**4.09 (1.22–13.69)**	**0.025***	3.95 (1.51–10.36)	0.005*	0.97 (0.45–2.09)	1.000
Cw*0102	12/21 (57.1)	9/29 (31.0)	161/485 (33.2)	2.96 (0.92–9.53)	0.086	2.68 (1.11–6.50)	0.033*	0.91 (0.40–2.03)	1.000
Cw*0702	7/21 (33.3)	4/29 (13.8)	73/485 (15.1)	3.13 (0.78–12.57)	0.166	2.82 (1.10–7.23)	0.034*	0.903 (0.31–2.67)	1.000
A*2402/Cw*0102	10/21 (47.6)	3/29 (10.3)		**7.88 (1.81–34.28)**	**0.007***				
A*3303	1/21 (4.8)	8/29 (27.6)	140/485 (28.9)	0.13 (0.02–1.15)	0.061	0.12 (0.02–0.93)	0.012*	0.94 (0.41–2.17)	1.000
Cw*0701	0/21 (0)	3/29 (10.3)	3/485 (0.6)		0.254		1.000	18.54 (3.57–96.36)	0.003*
Cw*0304	3/21 (14.3)	11/29 (37.9)	62/485 (12.8)	0.27 (0.07–1.14)	0.110	1.14 (0.33–3.97)	0.743	4.17 (1.88–9.24)	0.001*
DRB1*1101	4/21 (19.0)	6/29 (20.7)	43/485 (8.9)	0.90 (0.22–3.70)	1.000	2.42 (0.78–7.51)	0.120	2.68 (1.04–6.94)	0.047*
B*1502[a]	0/21 (0)	1/29 (3.4)	2/485 (0.4)		1.000		1.000	8.63 (0.76–98.02)	0.160
A*3101[a]	1/21 (4.8)	2/29 (6.9)	50/485 (10.3)	0.68 (0.06–7.97)	1.000	0.44 (0.06–3.31)	0.711	0.64 (0.15–2.79)	0.757
B*1511[a]	2/21 (9.5)	0/29 (0)	19/485 (3.9)		0.171	2.58 (0.56–11.89)	0.215		0.616
A*3001[b]	0/21 (0)	2/29 (6.9)	31/485 (6.4)		0.503		0.631	1.09 (0.25–4.77)	0.709
B*1302[b]	0/21 (0)	2/29 (6.9)	32/485 (6.6)		0.503		0.387	1.05 (0.24–4.61)	1.000
B*5801[b]	2/21 (9.5)	4/29 (13.8)	59/485 (12.2)	0.66 (0.11–3.98)	1.000	0.76 (0.17–3.35)	1.000	1.16 (0.39–3.44)	0.770
DRB1*1301[b]	0/21 (0)	1/29 (3.4)	9/485 (1.9)		1.000		1.000	1.89 (0.23–15.44)	0.443
DQB1*0609[b]	1/21 (4.8)	2/29 (6.9)	36/485 (7.4)	0.68 (0.06–7.97)	1.000	0.62 (0.08–4.78)	1.000	0.92 (0.21–4.04)	1.000

Bold values are the most significant risk allele or haplotype for lamotrigine-induced MPE.
MPE, maculopapular eruption; LTG, lamotrigine.
*p-Value < 0.05.
[a]Previously reported to be associated with carbamazepine-induced SCARs.
[b]Previously reported to be associated with LTG-induced MPE.

When comparing the number of patients possessing both the A*2402 and the Cw*0102 alleles between the LTG-MPE and the LTG-tolerant group, the association between the HLA genotype and LTG-induced MPE became more significant (OR 7.88). However, the OR of this association was not as high as the OR obtained for associations between specific HLA subtypes and the SCARs.[4,7] We hypothesized that this difference was due to the different incidence of SCARs versus MPE. Considering that LTG-induced MPE occurs in 5–10% of the patients,[2] it is likely that, in the case of an association with a particular HLA subtype, the responsible allele would be a relatively common one. Indeed, the three risk factor alleles identified in our study were common alleles (with a frequency ranging from 8.3% to 21.7%) among the Korean population.[5] Previously, a significant association between HLA-A*2402 allele and CBZ-induced SJS/TEN in Han Chinese has been reported[13]; however, one meta-analysis study has reported A*2402 allele as a protective marker for bullous lesions in Asians with CBZ-induced cADRs.[7] In addition, A*2402 has been suggested as a protective marker against the cross-reactivity of aromatic AED-induced cADR in a Chinese population.[14] One must keep in mind that 90% of the patients in this study (54 of 60; 90%) had a history of MPE and 40% of the patients (24 of 60) carried this allele. Considering the frequency of the A*2402 allele in the Chinese population (10.5%), we can assume that the A*2402 allele was found more frequently in MPE patients. Among the protective alleles, the HLA-A*3303 allele has been suggested to exert a protective effect on LTG-induced MPE.[10] None of the HLA-B alleles were significantly associated with LTG-induced MPE in our study, which is in accordance with the results from a previous report studying the Han Chinese population.[2]

Our study is meaningful because we identified HLA-related genetic risk factors for LTG-induced MPE in the Korean population for the first time. Considering the ethnicity-related differences in the HLA-related genetic susceptibility, results obtained from each ethnic group are meaningful by themselves. Moreover, the LTG-tolerant patients included in our study were selected following the strict criteria. By selecting the obviously tolerant patients, we could identify an additional allele (Cw*0701) that possibly protects the patients against LTG-induced MPE. Finally, we analyzed the association between HLA-induced MPE and the major histocompatibility complex (MHC) class II genes (*HLA-DRB1* and *HLA-DQB1* gene). It is suggested that maculopapular reactions are related mainly to the MHC class II molecules, whereas bullous formations are related mainly to the MHC class I genes.[15] Therefore, we expected to identify a specific MHC class II–related HLA subtype that would be associated with LTG-induced MPE. However, neither of the MHC class II genes (HLA-DRB1 or DQB1) has demonstrated any significant association.

In conclusion, our data suggest that several HLA alleles are associated with LTG-induced MPE. The coexistence of the HLA-A*2402 and Cw*0102 alleles was the strongest risk factor for LTG-induced MPE, whereas the A*3303 mutation was protective. The known presence of the risk alleles in patients should inspire great caution with regard to the prescription of LTG. Additional studies with larger number of patients and studies aimed at identifying non–HLA-related genetic risk factors (e.g., single nucleotide polymorphism (SNP), mitochondrial DNA haplotype) in relation to LTG-induced MPE should be performed in the near future.

Acknowledgments

This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI13C1558). S.K.L. was supported by Seoul National University Hospital (0320140160).

Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

References

1. Arif H, Buchsbaum R, Pierro J, et al. Comparative effectiveness of 10 antiepileptic drugs in older adults with epilepsy. *Arch Neurol* 2010;67:408–415.
2. Shi YW, Min FL, Liu XR, et al. HLA-B alleles and lamotrigine-induced cutaneous adverse drug reactions in the Han Chinese population. *Basic Clin Pharmacol Toxicol* 2011;109:42–46.
3. 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;48:1015–1018.
4. Bloch KM, Sills GJ, Pirmohamed M, et al. Pharmacogenetics of antiepileptic drug-induced hypersensitivity. *Pharmacogenomics* 2014;15:857–868.
5. Lee K, Oh D, Lee C, et al. Allelic and haplotypic diversity of HLA-A,-B,-C,-DRB1, and-DQB1 genes in the Korean population. *Tissue Antigens* 2005;65:437–447.
6. Kim S-H, Lee KW, Song W-J, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res* 2011;97:190–197.
7. Grover S, Kukreti R. HLA alleles and hypersensitivity to carbamazepine: an updated systematic review with meta-analysis. *Pharmacogenet Genomics* 2014;24:94–112.
8. Kaniwa N, Saito Y, Aihara M, et al. HLA-B* 1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 2010;51:2461–2465.
9. Ozeki T, Mushiroda T, Yowang A, 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;20:1034–1041.
10. Li L-J, Hu F-Y, Wu X-T, et al. Predictive markers for carbamazepine and lamotrigine-induced maculopapular exanthema in Han Chinese. *Epilepsy Res* 2013;106:296–300.
11. Kazeem GR, Cox C, Aponte J, et al. High-resolution HLA genotyping and severe cutaneous adverse reactions in lamotrigine-treated patients. *Pharmacogenet Genomics* 2009;19:661–665.
12. Fricke-Galindo I, Martínez-Juárez IE, Monroy-Jaramillo N, et al. HLA-A* 02: 01: 01/-B* 35: 01: 01/-C* 04: 01: 01 haplotype associated with lamotrigine-induced maculopapular exan-

thema in Mexican Mestizo patients. *Pharmacogenomics* 2014;15: 1881–1891.
13. Shi YW, Min FL, Qin B, et al. Association between HLA and Stevens-Johnson Syndrome induced by Carbamazepine in Southern Han Chinese: genetic markers besides B* 1502? *Basic Clin Pharmacol Toxicol* 2012;111:58–64.
14. Wang W, Hu F-Y, Wu X-T, et al. Genetic susceptibility to the cross-reactivity of aromatic antiepileptic drugs-induced cutaneous adverse reactions. *Epilepsy Res* 2014;108:1041–1045.
15. Naisbitt DJ. Drug hypersensitivity reactions in skin: understanding mechanisms and the development of diagnostic and predictive tests. *Toxicology* 2004;194:179–196.