



## Letter

## HLA-A\*31:01 and lamotrigine-induced severe cutaneous adverse drug reactions in a Korean population

Lamotrigine (LTG) was first synthesized in the early 1980s and approved by the US Food and Drug Administration in 1994. Since then, it has been used worldwide as an effective anticonvulsant and as a mood stabilizer. However, LTG can cause adverse reactions including cutaneous adverse drug reactions with approximately 10% probability.<sup>1</sup> Severe cutaneous adverse reactions (SCARs) are the most serious form and include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS). Although SCAR is clinically important because of its high mortality, there are currently no predictive markers for LTG-induced SCAR. Recent advances in pharmacogenomics have found that certain HLA alleles are significantly associated with SCARs caused by drugs, such as carbamazepine and allopurinol.<sup>2–4</sup> In addition, several studies have described the economic efficiency of genetic screening before prescribing a specific drug.<sup>3</sup> Based on these findings, we performed HLA genotyping to identify HLA alleles associated with the risk for LTG-induced SCAR in a Korean population.

Patients were enrolled in 4 hospitals in Korea (Seoul National University Hospital, Seoul National University Bundang Hospital, Ajou University Hospital, and Asan Medical Center), which are members of the Pharmacogenomics Research Center for Adverse Drug Reaction in Korea. LTG was assessed as causative of SCAR with a grade of “certain” or “probable” on the World Health Organization Uppsala Monitoring Center causality assessment system. Patients were excluded if their clinical data were incomplete or the cause for SCAR was indeterminable. SJS, SJS-TEN overlap, and TEN were diagnosed according to the range of detached surface area (<10%, 10–30%, and >30%, respectively). DRESS was diagnosed using the criteria proposed by the RegiSCAR group.<sup>5</sup> All clinical evaluations were performed by allergy specialists with more than 10 years of experience in drug allergy consultation. Genomic DNA was extracted from peripheral blood mononuclear cells of patients. HLA genotyping was performed using polymerase chain reaction sequence-specific oligonucleotide probes according to the established protocols.<sup>6</sup>

We used 2 different control groups: a cohort consisting of LTG-tolerant patients and a cohort of individuals from the general Korean population. HLA genotyping data of 29 LTG-tolerant subjects were described in our previous study.<sup>1</sup> In addition, HLA allele frequencies of individuals from the general Korean population were obtained from a previous study that provided serologic HLA typing results of 485 apparently unrelated healthy Korean individuals.<sup>6</sup> The Fisher exact test was performed to evaluate differences in

HLA allele frequencies between the LTG-induced SCAR group and the 2 control groups. Multiple comparisons were corrected using Bonferroni correction. *P* values less than .05 were considered significant. The odds ratio (OR) and 95% confidence interval (95% CI) also were calculated. All statistical analyses were performed using PASW Statistics 18.0 (SPSS Inc, Chicago, Illinois). This study was approved by the institutional review board of each hospital and written informed consent was obtained from all participants.

Eighteen patients with LTG-induced SCAR were recruited for this study. We found that the frequency of the HLA-A\*31:01 allele was significantly higher in the LTG-induced SCAR group compared with the LTG-tolerant group (OR 11.43; 95% CI 1.95–59.77; *P* = .0037) and the control group of the general Korean population (OR 7.27; 95% CI 2.63–18.45; *P* = .00034) and the latter remained significant after Bonferroni correction for multiple comparisons (Table 1).

We also found that the frequency of the HLA-Cw\*03:04 allele was lower in the LTG-induced SCAR cohort compared with the LTG-tolerant control group (OR 0.09; 95% CI 0.01–0.83; *P* = .017). In addition, allele frequencies of HLA-A\*24:02, HLA-B\*13:02, HLA-B\*35:03, HLA-B\*52:01, HLA-B\*57:01, HLA-Cw\*04:01, HLA-Cw\*12:02, and HLA-Cw\*12:03 were higher in patients from the LTG-induced SCAR cohort than in the LTG-tolerant group, which included individuals from the general Korean population. However, these findings were not significant after Bonferroni correction (Table 1).

Our finding that HLA-A\*31:01 might be a risk allele for LTG-induced SCAR was in contrast to previous studies that did not find evidence of an association of this allele in other ethnic populations, which suggests that HLA-A\*31:01 might be a Korean-specific allele associated with the risk for LTG-induced SCAR. HLA-B\*38 was the first allele identified to be significantly associated with LTG-induced SCAR in patients with European ancestry.<sup>4</sup> Interestingly, HLA-B\*15:02, which is a well-known risk allele of carbamazepine-induced SCAR in Han Chinese and South East Asians,<sup>3</sup> also was reported to be significantly associated with LTG-induced SCAR in Han Chinese.<sup>7</sup> However, there have been inconsistent findings in other ethnic populations. HLA-A\*68:01, HLA-B\*58:01, HLA-C\*07:18, HLA-DQB1\*06:09, and HLA-DRB1\*13:01 have been identified as important alleles in patients with European ancestry,<sup>8</sup> whereas HLA-B\*40:02, HLA-B\*57:01, and HLA-B\*58:01 have been significantly associated with LTG-induced SCAR in Mestizo Mexicans.<sup>9</sup>

In the present study, the HLA-A\*31:01 allele was identified as a risk allele of LTG-induced SCAR in Koreans. In Korea, HLA-A\*31:01 also was significantly increased in patients with carbamazepine-induced SCAR compared with the general Korean population.<sup>2</sup> Taken together, HLA-A\*31:01 might be a common risk allele of

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**Table 1**Summary of 4-Digit HLA Alleles With a P Value Less Than .05 for Combined Severe Cutaneous Adverse Drug Reactions (Before Bonferroni Correction)<sup>a</sup>

| HLA allele | Phenotype frequency (%) |                      |                           | Allele frequency (%) |                      |                           | SCAR vs LTG-tolerant control |                    | SCAR vs Korean general population control |                     |
|------------|-------------------------|----------------------|---------------------------|----------------------|----------------------|---------------------------|------------------------------|--------------------|-------------------------------------------|---------------------|
|            | SCAR                    | LTG-tolerant control | Korean general population | SCAR                 | LTG-tolerant control | Korean general population | P value <sup>b</sup>         | OR (95% CI)        | P value <sup>b</sup>                      | OR (95% CI)         |
| A*24:02    | 11/18 (61.1)            | 11/29 (37.9)         | 188/485 (38.8)            | 11/36 (30.5)         | 13/58 (22.4)         | 210/970 (21.6)            | .14                          | 2.57 (0.77–8.61)   | .0083                                     | 2.48 (0.94–6.52)    |
| A*31:01    | 8/18 (44.4)             | 2/29 (6.9)           | 50/485 (10.3)             | 8/36 (22.2)          | 2/58 (3.4)           | 52/970 (5.4)              | .0037 <sup>c</sup>           | 11.43 (1.95–59.77) | .00034 <sup>d</sup>                       | 7.27 (2.63–18.45)   |
| B*13:02    | 5/18 (27.8)             | 2/29 (6.9)           | 32/485 (6.6)              | 5/36 (13.9)          | 2/58 (3.4)           | 34/970 (3.5)              | .089                         | 5.19 (0.89–30.43)  | .0069                                     | 5.44 (1.82–16.23)   |
| B*35:03    | 2/18 (11.1)             | 0/29 (0)             | 4/485 (0.8)               | 2/36 (5.6)           | 0/58 (0)             | 4/970 (0.4)               | .14                          | NA                 | .016                                      | 15.03 (2.56–88.16)  |
| B*52:01    | 4/18 (22.2)             | 1/29 (3.4)           | 27/485 (5.6)              | 4/36 (11.1)          | 1/58 (1.7)           | 27/970 (2.8)              | .063                         | 8.00 (0.81–78.47)  | .020                                      | 4.84 (1.49–15.73)   |
| B*57:01    | 2/18 (11.1)             | 0/29 (0)             | 2/485 (0.4)               | 2/36 (5.6)           | 0/58 (0)             | 2/970 (0.2)               | .14                          | NA                 | .0069                                     | 30.19 (3.99–228.05) |
| Cw*03:04   | 1/18 (5.6)              | 11/29 (37.9)         | 62/485 (12.8)             | 1/36 (2.8)           | 12/58 (20.7)         | 67/970 (6.9)              | .017                         | 0.09 (0.01–0.83)   | .49                                       | 0.40 (0.05–3.07)    |
| Cw*04:01   | 6/18 (33.3)             | 3/29 (10.3)          | 62/485 (12.8)             | 6/36 (16.7)          | 3/58 (5.2)           | 64/970 (6.6)              | .068                         | 4.33 (0.92–20.32)  | .024                                      | 3.41 (1.24–9.42)    |
| Cw*12:02   | 4/18 (22.2)             | 1/29 (3.4)           | 24/485 (4.9)              | 4/36 (11.1)          | 1/58 (1.7)           | 24/970 (2.5)              | .063                         | 8.00 (0.82–78.47)  | .014                                      | 5.49 (1.68–17.94)   |
| Cw*12:03   | 2/18 (11.1)             | 0/29 (0)             | 5/485 (1.0)               | 2/36 (5.6)           | 0/58 (0)             | 5/970 (0.5)               | .14                          | NA                 | .023                                      | 12.00 (2.16–66.60)  |

Abbreviations: CI, confidence interval; LTG, lamotrigine; NA, not applicable; OR, odds ratio; SCAR, severe cutaneous adverse reaction.

<sup>a</sup>P values and ORs were calculated from phenotype frequencies.<sup>b</sup>P value by Fisher exact test (before Bonferroni correction).<sup>c</sup>P value after Bonferroni correction (multiplied by 64; 32 loci × 2 tests) = .237.<sup>d</sup>P value after Bonferroni correction (multiplied by 64; 32 loci × 2 tests) = .021.

carbamazepine-induced and LTG-induced SCAR in Koreans with HLA-B\*1502 is in Han Chinese. The difference in risk alleles between the Korean and Han Chinese groups reminds us of a well-known idea that the association between the HLA allele and drug-induced SCAR is specific to ethnicity. Interestingly, a decreased frequency of HLA-Cw\*03:04 was associated with LTG-induced SCAR, which could indicate the presence of protective alleles. In this study, we examined only HLA class I (HLA-A, B, and Cw). However, associations between HLA class II (HLA-DR, DP, and DQ) and LTG-induced SCAR need to be evaluated, because a previous report showed that LTG was present on HLA-DR and HLA-DQ and native LTG without metabolism was sufficient for presentation to T cells.<sup>10</sup>

In conclusion, we found evidence for a significant association between the HLA-A\*31:01 allele and risk for LTG-induced SCAR in Korean patients. Our study is the largest such study of LTG-induced SCAR in Koreans providing the statistical power necessary to identify HLA alleles associated with risk for LTG-induced SCAR.

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## References

- 1 Moon J, Park HK, Chu K, et al. The HLA-A\*2402/Cw\*0102 haplotype is associated with lamotrigine-induced maculopapular eruption in the Korean population. *Epilepsia*. 2015;56:e161–e167.
- 2 Kim SH, Lee KW, Song WJ, et al. Carbamazepine-induced severe cutaneous adverse reactions and HLA genotypes in Koreans. *Epilepsy Res*. 2011;97:190–197.
- 3 Chen Z, Liew D, Kwan P. Real-world efficiency of pharmacogenetic screening for carbamazepine-induced severe cutaneous adverse reactions. *PLoS One*. 2014;9:e96990.
- 4 Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenet Genomics*. 2008;18:99–107.
- 5 Eshki M, Allanore L, Musette P, et al. Twelve-year analysis of severe cases of drug reaction with eosinophilia and systemic symptoms: a cause of unpredictable multiorgan failure. *Arch Dermatol*. 2009;145:67–72.
- 6 Lee KW, Oh DH, Lee C, Yang SY. Allelic and haplotypic diversity of HLA-A, -B, -C, -DRB1, and -DQB1 genes in the Korean population. *Tissue Antigens*. 2005;65:437–447.
- 7 Zeng T, Long YS, Min FL, Liao WP, Shi YW. Association of HLA-B\*1502 allele with lamotrigine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese subjects: a meta-analysis. *Int J Dermatol*. 2015;54:488–493.
- 8 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.
- 9 Fricke-Galindo I, Martinez-Juarez 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 exanthema in Mexican Mestizo patients. *Pharmacogenomics*. 2014;15:1881–1891.
- 10 Naisbitt DJ, Farrell J, Wong G, et al. Characterization of drug-specific T cells in lamotrigine hypersensitivity. *J Allergy Clin Immunol*. 2003;111:1393–1403.