学 位 論 文 の 要 旨

氏名　新原寛之

学 位 論 文 名　HLA-A31 Strongly Associates With Carbamazepine-Induced Adverse Drug Reactions but Not With Carbamazepine-Induced Lymphocyte Proliferation in a Japanese Population

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著 者 名　Hiroyuki Niihara, Takeyasu Kakamu, Yasuyuki Fujita, Sakae Kaneko, Eishin Morita

論 文 内 容 の 要 旨

INTRODUCTION

Carbamazepine (CBZ) has been widely used as antiepileptic drug. CBZ is the most frequent culprit drug for life-threatening severe cutaneous adverse drug reactions (ADRs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DIHS). Since a strong association between HLA-B*1502 and CBZ-induced SJS/TEN was reported in Han Chinese residing in Taiwan, intensive studies have focused on the association between HLA class I allele and ADRs. An association between HLA-B*1502 and CBZ-induced SJS/TEN has been confirmed in South East Asian populations, but an association has not been seen in Caucasians. In addition, no HLA-B*1502 carriers were detected in drug-unspecified SJS/TEN patients in a Japanese population. We conducted a case-control study to determine HLA types associated with CBZ-induced ADRs in a Japanese population. In addition, CBZ-induced lymphocyte proliferation was evaluated to determine whether HLA types are associated with lymphocyte activation, because T-cell-mediated allergic reaction is likely to be involved in the pathogenesis of ADRs.

MATERIALS AND METHODS

All patients were recruited from Shimane University Hospital between April 2005 and February 2011. These included 15 patients with CBZ-induced ADRs and 33 patients who had been receiving CBZ for more than 3 months without drug eruption. CBZ-induced ADRs were determined by medical history indicating that symptoms

occurred within 3 months after starting CBZ administration and that the symptoms resolved upon withdrawal of this drug.

For HLA typing of the patients DNA was extracted from peripheral blood. Low-resolution HLA typing was performed using the reverse sequence-specific oligonucleotide with polymerase chain reaction method. High-resolution HLA-B genotyping was determined using the polymerase chain reaction-sequence based typing method. CBZ-induced lymphocyte proliferation was assayed with peripheral blood mononuclear cells isolated from whole blood. Statistical analysis of the differences in each allele frequency among patients with ADRs and CBZ-tolerant patients was performed by Fisher's exact test.

RESULTS AND DISCUSSION

Low-resolution HLA typing of the patients revealed that HLA-A11, HLA-A31 and HLA-B51 are significantly frequent in the CBZ-induced ADR patients. The odds ratio (OR) of HLA-A31 was the highest (OR 11.200, 95%CI 2.668–47.105, p= 0.001). One of the three SJS/TEN patients, eight of the nine DIHS patients, and one of the three patients with maculopapular eruption/erythema multiforme exudativum had HLA-A31. High resolution HLA genotyping of HLA-B locus showed that HLA-B*5101 appeared significantly higher in the CBZ-induced ADR patients but HLA-B*1502 was not found in both the CBZ-induced ADR patients and the CBZ-tolerant patients.

When CBZ-induced lymphocyte proliferation was performed, mean stimulation index (SI) of CBZ-induced ADR patients (382.1 ± 295.1%, n = 15) was significantly high compared with that of CBZ-tolerant patients (125.3 ± 29.5%, n = 32, $P < 0.001$). The mean SI was not significantly different between subjects with and without the HLA-A31 allele in both CBZ-induced ADR patients and CBZ-tolerant patients.

On the basis of previous reports of HLA associated with CBZ-induced ADR in Japanese and Caucasian population, we confirmed the association between HLA-A*3101 and CBZ-induced ADRs, especially CBZ-induced DIHS. HLA-B*1502, which is associated with CBZ-induced ADRs in Han Chinese and other Asian population, was not found in either CBZ-induced ADR patients or CBZ-tolerant patients. Altogether, HLA-B*1502 is strongly associated with CBZ-induced SJS/TEN in Asians, whereas HLA-A*3101 is well associated with CBZ-induced ADRs in Japanese and Caucasian.

The reason for the diversity of HLA association in CBZ-induced ADRs among

races is unclear. It is possible that common amino acid sequences between HLA-B*1502 and HLA-A*3101 associates with CBZ-induced ADRs. Although some amino acid sequences are common between HLA-B*1502 and HLA- A*3101 (No 61, 64, 68, 72, 75, 78), each of amino acid sequence of HLA-A*240201 is also the same as well, which is one of the major Japanese HLA alleles. No specific amino acid was found in the amino acid sequence of α domain of HLA-A*3101 and HLA-B*1502. Association of HLA alleles differing in races with CBZ-induced ADRs may be due to common three-dimensional structure, whose commonality is independent of amino acid sequences.

Another possibility for an association between the two HLA types and ADR is a linkage disequilibrium phenomenon in the HLA locus. Near the HLA gene, several inflammatory cytokine genes are mapped, such as IFN-γ, TNF-ß. However, a recent detailed genome-wide association study concerning CBZ-induced ADR indicated that the CBZ-induced ADR gene is located at the HLA locus area; thus, it is not likely that another gene with polymorphisms caused CBZ-induced ADR.

A third possibility is that HLA-B*1502 is associated with SJS/TEN, but not with DIHS or MPS, whereas HLA-A*3101 is associated with DIHS, but not with SJS/TEN. Although HLA-B*1502 was found to be specific to CBZ-induced SJS/TEN in Han Chinese, no association was seen in patients with CBZ-induced hypersensitivity syndrome or maculopapular eruption. In addition, no association with HLA-B*1502 was confirmed in Caucasian patients with hypersensitivity syndrome. In the present study, we found an association between HLA-A31 and DIHS, but only one of three patients with SJS/TEN had HLA-A31, supporting this hypothesis.

HLA is well documented to be associated with some chronic inflammatory diseases. In the present study we also tested the association between HLA-A*3101 and SI of CBZ-induced lymphocyte proliferation. We failed to demonstrate the HLA-A31-associated enhancement of lymphocyte-proliferation, although we were able to confirm strong lymphocyte activation with CBZ in the patient group.

CONCLUSION

In the present study, we confirmed a strong association between HLA-A31 and CBZ-induced ADRs in a Japanese population. However, HLA-A31 does not determine CBZ-induced lymphocyte proliferation.