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Association of HLA class I and II gene polymorphisms with acetaminophen-related Stevens–Johnson syndrome with severe ocular complications in Japanese individuals

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Abstract

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute-onset mucocutaneous diseases induced by infectious agents and/or inciting drugs. We have reported that the main causative drugs for SJS/TEN with severe ocular complications (SOC) were cold medicines, including multi-ingredient cold medications and nonsteroidal anti-inflammatory drugs (NSAIDs). Moreover, we also reported that acetaminophen is the most frequent causative drug in various cold medicines. In this study, we focused on acetaminophen-related SJS/TEN with SOC and analyzed *HLA-class II (HLA-DRB1, DQB1)* in addition to *HLA-class I (HLA-A, B, C)*. We studied the histocompatibility antigen genes *HLA-DRB1* and *DQB1* in addition to *HLA-A, B*, and *C* in 80 Japanese patients with acetaminophen-related SJS/TEN with SOC. We performed polymerase chain reaction amplification followed by hybridization with sequence-specific oligonucleotide probes (PCR-SSO) using commercial bead-based typing kits. We also used genotyped data from 113 healthy volunteers for *HLA-DRB1* and *DQB1*, and 639 healthy volunteers for *HLA-A, B, and C*. *HLA-DRB1*08:03* and *DRB1*12:02* were associated with acetaminophen-related SJS/TEN with SOC, although the results ceased to be significant when we corrected the *p*-value for the number of alleles detected. *HLA-A*02:06* was strongly associated with acetaminophen-related SJS/TEN with SOC (carrier frequency: $p = 4.7 \times 10^{-12}$, $Pc = 6.6 \times 10^{-11}$, OR = 6.0; gene frequency: $p = 8.0 \times 10^{-13}$, $Pc = 1.1 \times 10^{-11}$, OR = 4.9). *HLA-B*13:01* (carrier frequency: $p = 2.0 \times 10^{-3}$, Pc = 0.042, OR = 4.1; gene frequency: $p = 2.2 \times 10^{-3}$, Pc = 0.047, OR = 3.9), *HLA-B*44:03* (carrier frequency: $p = 2.1 \times 10^{-3}$, Pc = 0.045, OR = 2.4) and *HLA-C*14:03* (carrier frequency: $p = 3.4 \times 10^{-3}$, Pc = 0.045, OR = 2.3) were also significantly associated, while *HLA-A*24:02* was inversely associated (gene frequency: $p = 6.3 \times 10^{-4}$, $Pc = 8.8 \times 10^{-3}$, OR = 0.5). Acetaminophen-related SJS/TEN with SOC was not associated with *HLA-class II (HLA-DRB1, DQB1)*. However, for acetaminophen-related SJS/TEN with SOC, we found an association with *HLA-B*13:01* and *HLA- C*14:03* in addition to *HLA-A*02:06* and *HLA-B*44:03*, which have been described previously.

Introduction

Stevens–Johnson syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin and the mucosa of the ocular surface, oral cavity, and genitals. Patients with extensive skin detachment and a poor prognosis have toxic epidermal necrolysis (TEN).

In the acute stage of SJS/TEN, approximately 50% of patients present with severe ocular lesions, such as severe

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conjunctivitis with pseudomembrane and ocular surface epithelial defects[1].

The mortality rate of SJS/TEN is high (3% for SJS and 27% for TEN)[2], although its reported annual incidence is only 1–6 per million individuals[1]. The extreme rarity of cutaneous and ocular surface reactions to drug therapies led us to suspect individual susceptibility.

While associations between SJS/TEN and many kinds of inciting drugs have been documented[3], we have reported that the main causative drugs for SJS/TEN with severe ocular complications (SOC) were cold medicines; approximately 80% of our SJS/TEN with SOC patients developed SJS/TEN within several days after taking cold medicines, including multi-ingredient cold medications and nonsteroidal anti-inflammatory drugs (NSAIDs), to combat the common cold[4–7]. Moreover, we also reported that acetaminophen is the most frequent causative drug ingredient in various cold medicines and that cold medicine-related SJS/TEN with SOC, including acetaminophen-related SJS/TEN with SOC, was significantly associated with *HLA-A*02:06* and *HLA-B*44:03* in Japanese individuals[6]. However, in a previous study in which we focused on cold medicines, we analyzed only *HLA-class I (HLA-A, B, and C)*.

On the other hand, Power et al.[8] reported that *HLA-DQB1*06:01* was associated with Caucasian patients with ocular complications of SJS.

In this study, we focused on acetaminophen-related SJS/TEN with SOC and analyzed *HLA-class II (HLA-DRB1, DQB1)* in addition to *HLA-class I (HLA-A, B, C)*.

Materials and methods

Patients

Our study was approved by the institutional review boards of Kyoto Prefectural University of Medicine, Kyoto, Japan, and the National Institute of Health Sciences, Kawasaki, Japan. All experimental procedures were conducted in accordance with the principles set forth in the Helsinki Declaration and Ethical Guidelines for Human Genome/Gene Analysis Research of Japan. The purpose of the study and the experimental protocols were explained to all participants, and their prior written informed consent was obtained.

Because ophthalmologists encounter patients not only in the acute stage but also in the chronic stage, it is not easy for ophthalmologists to render a differential diagnosis of SJS or TEN when patients present in the chronic stage because the vesiculobullous skin lesions evident in the acute stage have healed by the chronic stage[5]. Thus, our ophthalmologic diagnosis of SJS/TEN was based on a confirmed history of acute-onset high fever, serious mucocutaneous illness with skin eruptions, and the involvement of at least 2 mucosal sites, including the ocular surface[4,6,7,9,10].

SJS/TEN patients with SOC in the acute stage often suffer severe ocular sequelae such as vision loss and very severe dry eye that prevent them from having a normal life[11]. We defined acute-stage SOC as a condition with severe conjunctivitis with pseudomembrane and epithelial defects on the ocular surface (cornea and/or conjunctiva)[12] and chronic-stage SOC as a condition with ocular sequelae such as severe dry eye, trichiasis, symblepharon, and conjunctival invasion into the cornea[11].

For HLA genotyping, we enrolled 80 Japanese SJS/TEN with SOC patients (64 of them were recruited by Kyoto Prefectural University of Medicine, and 16 of them were recruited by the Japan Severe Adverse Reactions research group (JSAR research group, mainly operated by the National Institute of Health Sciences)). The average patient age was 38.9 ± 17.6 (SD) years, and the average onset age was 30.1 ± 16.5 (SD) years; the male:female ratio was 32:48. Note that the results of HLA class I (HLA-A, B, and C types) from 73 cases of acetaminophen-related SJSTEN patients with SOC were reported previously[6].

Controls

We used the genotyped data of 113 healthy volunteer blood donors for *HLA class II (DRB1, DQB1)* and of 639 healthy volunteers for *HLA class I (A, B, C)*. All volunteers were Japanese residing in Japan. They have been used in our previous study[6,9].

HLA genotyping

We studied the histocompatibility antigen genes *HLA-A, B, C, DRB1*, and *DQB1* of 80 Japanese acetaminophen-related SJS/TEN with SOC patients. These alleles were detected by the PCR-Luminex typing method using the WAKFlow HLA Typing Kit (Wakunaga, Hiroshima) as previously reported[6,9,13]. Genotype determination and data analysis were performed automatically using the WAKFlow typing software.

Statistical methods

We compared the carrier frequency of individual *HLA* alleles in our patients and controls based on the dominant model using Fisher's exact test (JMP version 11 software; SAS Institute Japan Ltd., Tokyo, Japan). Each allele was assessed as an independent variable, and separate p-values were calculated. A p-value of <0.05 was regarded as significant. In addition, the p-values were corrected for the number of alleles tested. The alleles with total numbers under 8 for *HLA-class II (DRB1, DQB1)* and under 21 for *HLA class I (A, B, C)* were included in others.

Results

Table 1 shows the results on *HLA-DRB1* alleles. Although the correction of the p-values for the number of

Table 1 Association between HLA class II and acetaminophen-related SJS/TEN with SOC

HLA-DRB1	Carrier frequency					Gene Frequency				
	Case	Control	*p*-value (Fisher)	Corrected *p*-value	OR (95% CI)	Case	Control	*p*-value (Fisher)	Corrected *p*-value	OR (95% CI)
*DRB1*08:03*	27.5% (22/80)	13.3% (15/113)	**0.0161**	0.258	2.5 (1.2–5.2)	15.0% (24/160)	7.1% (16/226)	**0.0168**	0.167	2.3 (1.2–4.5)
*DRB1*12:02*	12.5% (10/80)	3.5% (4/113)	**0.0239**	0.382	3.9 (1.2–12.9)	6.3% (10/160)	1.8% (4/226)	**0.0265**	0.269	3.7 (1.1–12.0)

OR odds ratio, *CI* confidence interval
Bold values indicates $p < 0.05$

alleles detected ($n = 16$) rendered the result not significant, *HLA-DRB1*08:03* (carrier frequency: $p = 0.016$, Pc = 0.26, OR = 2.5; gene frequency: $p = 0.017$, Pc = 0.17, OR = 2.3) and *DRB1*12:02* (carrier frequency: $p = 0.024$, Pc = 0.38, OR = 3.9; gene frequency: $p = 0.027$, Pc = 0.27, OR = 3.7) were associated with acetaminophen-related SJS/TEN with SOC. There was also no association between *HLA-DQB1* and acetaminophen-related SJS/TEN with SOC (Supplementary Table 1).

As shown in Table 2a, *HLA-A*02:06* was strongly associated with acetaminophen-related SJS/TEN with SOC (carrier frequency: $p = 4.7 \times 10^{-12}$, Pc = 6.6×10^{-11}, OR = 6.0; gene frequency: $p = 8.0 \times 10^{-13}$, Pc = 1.1×10^{-11}, OR = 4.9). *HLA-A*24:02* was inversely associated (carrier frequency: $p = 5.3 \times 10^{-3}$, Pc = 0.074, OR = 0.5; gene frequency: $p = 6.3 \times 10^{-4}$, Pc = 8.8×10^{-3}, OR = 0.5). *HLA-A*33:03* was also associated (carrier frequency: $p = 0.011$, Pc = 0.16, OR = 2.1; gene frequency: $p = 0.12$, Pc = 0.16, OR = 2.0), and *HLA-A*11:01* (carrier frequency: $p = 0.024$, Pc = 0.34, OR = 0.4; gene frequency: $p = 0.037$, Pc = 0.52, OR = 0.4) *and A*26:01* (gene frequency: $p = 0.047$, Pc = 0.65, OR = 0.4) were inversely associated, but the association ceased to be significant when we corrected the *p*-value for the number of alleles detected ($n = 14$).

Table 2b shows the results on *HLA-B alleles*. *B*13:01* (carrier frequency: $p = 2.0 \times 10^{-3}$, Pc = 0.042, OR = 4.1; gene frequency: $p = 2.2 \times 10^{-3}$, Pc = 0.047, OR = 3.9), and *HLA-B*44:03* (carrier frequency: $p = 2.1 \times 10^{-3}$, Pc = 0.045, OR = 2.4; gene frequency: $p = 3.7 \times 10^{-3}$, Pc = 0.078, OR = 2.1) was significantly associated. *HLA-B*46:01* was also associated (carrier frequency: $p = 0.025$, Pc = 0.53, OR = 2.2; gene frequency: $p = 0.030$, Pc = 0.64, OR = 2.1), and *HLA-B*15:01* (carrier frequency: $p = 4.8 \times 10^{-3}$, Pc = 0.10, OR = 0.3; gene frequency: $p = 4.7 \times 10^{-3}$, Pc = 0.98, OR = 0.3) and *B*52:01* (carrier frequency: $p = 0.014$, Pc = 0.30, OR = 0.4; gene frequency: $p = 0.021$, Pc = 0.43, OR = 0.4) were inversely associated, although the results ceased to be significant when we corrected the *p*-value for the number of alleles detected ($n = 21$).

Table 2c shows the results for *HLA-C alleles*. *HLA-C*14:03* (carrier frequency: $p = 3.4 \times 10^{-3}$, Pc = 0.045, OR = 2.3; gene frequency: $p = 6.3 \times 10^{-3}$, Pc = 0.083, OR = 2.0) was significantly associated. *HLA-C*03:04* was also associated (carrier frequency: $p = 0.048$, Pc = 0.63, OR = 1.7), and *HLA-C*12:02* was inversely associated (carrier frequency: $p = 0.014$, Pc = 0.19, OR = 0.4; gene frequency: $p = 0.021$, Pc = 0.27, OR = 0.4), although the results ceased to be significant when we corrected the *p*-value for the number of alleles detected ($n = 13$). The results of *HLA-class I (HLA-A, B, C)* are shown in Supplementary Table 2.

Table 2 Association between HLA class I and acetaminophen-related SJS/TEN with SOC

	Carrier frequency					Gene frequency				
	Case	Control	*p*-value (Fisher)	corrected *p*-value	OR (95% CI)	Case	Control	*p*-value (Fisher)	corrected *p*-value	OR (95% CI)
a										
HLA-A										
A*02:06	48.8% (39/80)	13.62% (87/639)	**4.71E−12**	**6.59E−11**	6.0 (3.7–9.9)	27.5% (44/160)	7.12% (91/1278)	**8.01E−13**	**1.12E−11**	4.9 (3.3–7.4)
A*11:01	7.5% (6/80)	17.21% (110/639)	**0.0239**	0.335	0.4 (0.2–0.9)	4.4% (7/160)	9.31% (119/1278)	**0.0372**	0.521	0.4 (0.2–1.0)
A*24:02	43.8% (35/80)	60.72% (388/639)	**5.31E−3**	0.074	0.5 (0.3–0.8)	23.8% (38/160)	37.32% (477/1278)	**6.25E−4**	**8.75E−3**	0.5 (0.4–0.8)
A*26:01	6.3% (5/80)	14.40% (92/639)	0.0543		0.4 (0.2–1.0)	3.1% (5/160)	7.43% (95/1278)	**0.0465**	0.651	0.4 (0.2–1.0)
A*33:03	25.0% (20/80)	13.46% (86/639)	**0.011**	0.155	2.1 (1.2–3.7)	13.1% (21/160)	7.12% (91/1278)	**0.0117**	0.163	2.0 (1.2–3.3)
b										
HLA-B										
B*13:01	11.3% (9/80)	2.97% (19/639)	**1.98E−3**	**0.0415**	4.1 (1.8–9.5)	5.6% (9/160)	1.49% (19/1278)	**2.23E−3**	**0.0468**	3.9 (1.8–8.9)
B*15:01	5.0% (4/80)	16.90% (108/639)	**4.77E−3**	0.100	0.3 (0.1–0.7)	2.5% (4/160)	8.61% (110/1278)	**4.68E−3**	0.982	0.3 (0.1–0.7)
B*44:03	30.0% (24/80)	15.02% (96/639)	**2.12E−3**	**0.0446**	2.4 (1.4–4.1)	15.0% (24/160)	7.67% (98/1278)	**3.74E−3**	0.0784	2.1 (1.3–3.4)
B*46:01	17.5% (14/80)	8.76% (56/639)	**0.0251**	0.527	2.2 (1.2–4.2)	8.8% (14/160)	4.46% (57/1278)	**0.0304**	0.640	2.1 (1.1–3.8)
B*52:01	8.8% (7/80)	19.87% (127/639)	**0.0144**	0.303	0.4 (0.2–0.9)	4.4% (7/160)	10.02% (128/1278)	**0.0205**	0.431	0.4 (0.2–0.9)
c										
HLA-C										
C*03:04	32.5% (26/80)	22.07% (141/639)	**0.0484**	0.629	1.7 (1.0–2.8)	16.9% (27/160)	11.89% (152/1278)	0.0759		1.5 (1.0–2.4)
C*12:02	8.8% (7/80)	19.87% (127/639)	**0.0144**	0.188	0.4 (0.2–0.9)	4.4% (7/160)	10.02% (128/1278)	**0.0205**	0.267	0.4 (0.2–0.9)
C*14:03	28.8% (23/80)	14.87% (95/639)	**3.44E−3**	**0.0447**	2.3 (1.4–3.9)	14.4% (23/160)	7.67% (98/1278)	**6.34E−3**	0.0825	2.0 (1.2–3.3)

OR odds ratio, *CI* confidence interval
Bold values indicates $p < 0.05$

Discussion

We previously reported that approximately 80% of our SJS/TEN with SOC patients developed SJS/TEN within several days after taking cold medicines, including multi-ingredient cold medications and NSAIDs, to combat the common cold[4,5,7,13]. More than half of SJS/TEN with SOC patients developed SJS after taking cold medicines in the Brazilian population[14]. Cold medicine, including NSAIDs, might be associated with SOC in SJS/TEN patients in the Korean population[15]. Moreover, 69% of SJS/TEN with SOC patients had a history of taking cold medicine before the onset of SJS/TEN in the Thai population[16].

Acetaminophen, also called paracetamol, is the most frequent causative drug for cold medicine-related SJS/TEN with SOC in Japanese[6] and Thai individuals[16]. On the other hand, dipyrone is the most frequent cause of cold medicine-related SJS/TEN with SOC in Brazil[14].

In this study, we analyzed both class I and class II HLA types focused on acetaminophen-related SJS/TEN with SOC and found that there was also no association between *HLA class II (HLA-DQB1, DQB1)* and acetaminophen-related SJS/TEN with SOC and confirmed the strong association with *HLA-A*02:06* and the significant association with *HLA-B*44:03*, as in our previous study[6]. Moreover, we also found associations with *HLA-B*13:01* and *HLA-C*14:03* and an inverse association with *HLA-A*24:02*.

Power et al.[8] reported that *HLA-DQB1*06:01* was associated with Caucasian patients with ocular complications of SJS. However, we could not detect an association between Japanese SJS/TEN and SOC and *HLA-DQB1*06:01*.

*HLA-A*02:06* was significantly associated with Japanese[6] and Korean[17] cold medicine-related SJS/TEN with SOC. On the other hand, Brazilian cold medicine-related SJS/TEN with SOC was significantly associated with *HLA-A*66:01* in individuals with both Pardo and European ancestry and *HLA-B*44:03* and *HLA-C*12:03* for European ancestry[14]. Moreover, cold medicine-related SJS/TEN with SOC in Thailand was significantly associated with the *HLA-B*44:03-HLA-C*07:01* haplotype, although their main causative drug is paracetamol[16]. Thus, there are ethnic differences in associated HLAs with cold medicine-related SJS/TEN with SOC.

Acetaminophen-associated HLA type might be quite similar to HLA associated with cold medicine-related SJS/TEN with SOC. The binding modes of acetaminophen, ibuprofen, and loxoprofen at the antigenic peptide-binding groove of the HLA-A∗02:06 molecule are different because their molecules are not similar, and their composite risk indexes are also different[18]. Thus, we suggest that the common function of cold medicines, such as acetaminophen and NSAIDs, is most important for the onset of SJS/TEN with SOC. The common function of cold medicines is a suppression function of prostaglandin E_2 (PGE_2) production, which suppresses mucocutaneous inflammation; PGE_2 acts at EP3 (PGE_2 receptor 3), which is one of the 4 receptors (EP1, EP2, EP3, EP4) for PGE_2, in the epidermis[19] and mucosal epithelium[10,20], negatively regulating mucocutaneous inflammation. Cold medicine, including acetaminophen, could downregulate inflammatory suppressing mechanism(s) by PGE_2 and might augment the abnormal immune response resulting in the induction of SJS/TEN with SOC[5,21].

Acetaminophen (paracetamol) is thought to be a safe drug and is widely prescribed for children with cold symptoms or is widely included in commercial cold medicines. However, for SJS/TEN with SOC, acetaminophen could be the main causative drug. Therefore, physicians should prescribe it with knowledge about SJS/TEN.

In summary, acetaminophen-related SJS/TEN with SOC was not associated with HLA-class II (HLA-DRB1, DQB1), but we found an association with HLA-B*13:01 and HLA- C*14:03 in addition to HLA-A*02:06 and HLA-B*44:03, which have been described previously.

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Conflict of interest

The authors declare that they have no conflict of interest.

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