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Findings by an International Collaboration on SJS/TEN With Severe Ocular Complications

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Stevens-Johnson Syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the skin and mucosa, e.g., the ocular surface, oral cavity, and genitals. In patients with extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). Not all, but some patients with SJS/TEN manifest severe ocular lesions. Approximately 50% of SJS/TEN patients diagnosed by dermatologists and in burn units suffer from severe ocular complications (SOC) such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects in the acute stage. In the chronic stage, this results in sequelae such as severe dry eye and visual disturbance. Before 2005, our group of Japanese scientists started focusing on ophthalmic SJS/TEN with SOC. We found that cold medicines were the main causative drugs of SJS/TEN with SOC and that in Japanese patients, *HLA-A*02:06* and *HLA-B*44:03* were significantly associated with cold medicine-related SJS/TEN with SOC (CM-SJS/TEN with SOC). We expanded our studies and joined scientists from Korea, Brazil, India, Taiwan, Thailand, and the United Kingdom in an international collaboration to detect the genetic predisposition for SJS/TEN with SOC. This collaboration suggested that in Japanese patients, cold medicines, including NSAIDs, were the main causative drugs, and that *HLA-A*02:06* was implicated in Japanese and Korean patients and *HLA-B*44:03* in Japanese-, Indian-, and European ancestry Brazilian patients. Our joint findings reveal that there are ethnic differences in the HLA types associated with SJS/TEN with SOC.

Keywords: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), severe ocular complications (SOC), HLA, cold medicine

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INTRODUCTION

Stevens-Johnson syndrome (SJS) is an acute inflammatory vesiculobullous reaction of the mucosa of the ocular surface, oral cavity, and genitals, and of the skin. In patients with extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). In the acute stage of SJS/TEN, approximately 50% of patients present with severe ocular lesions such as severe conjunctivitis with pseudomembrane and ocular surface epithelial defects (1).

Ophthalmologists encounter patients not only in the acute- but also the chronic stage. Dermatologists, on the other hand, tend to see SJS/TEN patients only in the acute stage, although in some countries such as France and Germany dermatologists also followed up the patients long time. Our ophthalmologic diagnosis of SJS/TEN was based on a confirmed history of acute-onset high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least two mucosal sites, including the ocular surface (2–9). SJS/TEN patients with severe ocular complications (SOC)

in the acute stage often develop sequelae such as vision loss and very severe dry eye that prevent their having a normal life (10).

We defined acute-stage SOC as a condition with severe conjunctivitis with pseudomembrane and epithelial defects on the ocular surface (cornea and/or conjunctiva) (11). Chronic-stage SOC was defined as a condition with sequelae such as severe dry eye, trichiasis, symblepharon, and conjunctival invasion into the cornea (**Figure 1A**) (10). Ophthalmologists tend to diagnose both SJS and TEN with SOC broadly as "ophthalmic SJS" (**Figure 1B**) (4).

Dermatologists and others reported anticonvulsants such as carbamazepine and allopurinol (a uric acid-lowering drug) as being the main SJS/TEN-inciting drugs (12), while Japanese dermatologists reported that NSAIDs and multi-ingredient cold medications were main causative drugs for SJS/TEN (13). HLA analyses have shown that a genetic predisposition plays a role in the response to disease-eliciting drugs. Carbamazepine-induced SJS/TEN manifested a very strong association with the *HLA-B*15:02* allele in Taiwanese Han Chinese patients (14), and the *HLA-A*31:01* allele was strongly associated with carbamazepine-induced SJS/TEN in Japanese- (15) and European patients (16), the HLA-B*57:01 allele was associated with carbamazepine-induced SJS/TEN in European patients (17). Allopurinol-induced SJS/TEN was strongly associated with *HLA-B* 58:01* in Han Chinese- (18), European ancestry- (19), and Japanese patients (20). Interestingly, not all patients with carbamazepine-induced SJS/TEN develop SOC (21). Allopurinol has been reported to elicit SJS/TEN without SOC (22).

We reported that about 80% of SJS/TEN with SOC patients seen at the Kyoto Prefectural University of Medicine developed SJS/TEN within several days after taking cold medicines (we recognized the onset of SJS/TEN when the patients had eruptions.) (8).

These included multi-ingredient cold medications and non-steroidal anti-inflammatory drugs (NSAIDs) (2, 4, 6, 8, 23). Our Brazilian collaborators found that 53% of their SJS/TEN with SOC patients had taken cold medicines (24) as had 69% of Thai patients with SJS/TEN with SOC (25), and 50% of Taiwanese patients (26). Our Korean collaborators suspected that NSAIDs and cold medicines were associated with SOC in their SJS/TEN patients (27). These observations suggest that such medicines are major causative drugs in SJS/TEN with SOC patients of different ethnicities.

This mini-review cites the results of our international collaborative efforts to identify the genetic predisposition for SJS/TEN with SOC.

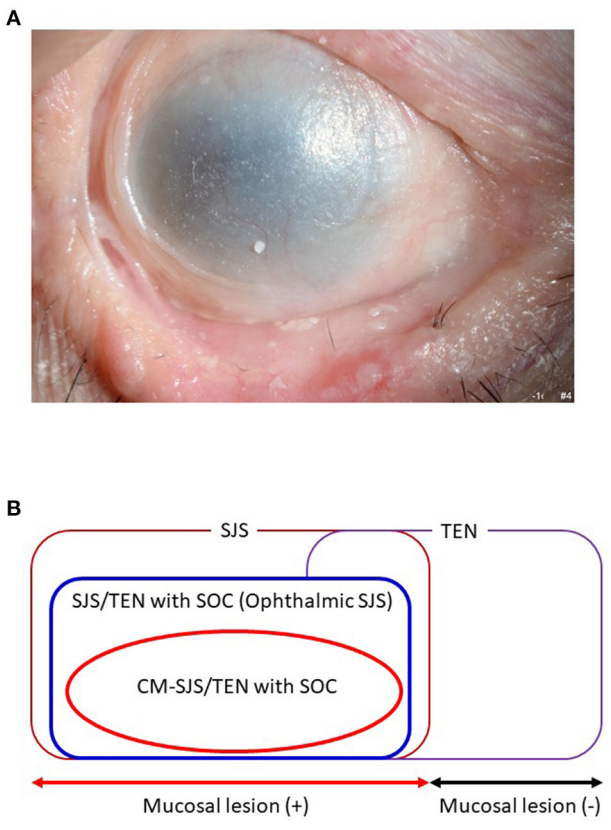

FIGURE 1 | (A) Ocular surface finding of SJS/TEN with SOC. **(B)** Ophthalmic SJS means SJS/TEN with SOC.

HLA TYPES ASSOCIATED WITH SJS/TEN WITH SOC

The extreme rarity of cutaneous and ocular surface reactions to drugs led us to suspect individual susceptibility. Therefore, we entered an international collaboration to analyze the association between HLA genotypes and SJS/TEN with SOC.

Japan

In 2007, our Japanese group first reported the HLA types associated with SJS/TEN with SOC; the ocular disease was strongly associated with *HLA-A*02:06* [40 patients, 113 controls; odds ratio (OR) = 5.1, $p = 0.00003$] (28). Finding that about 80% of our Japanese SJS/TEN with SOC patients developed SJS/TEN after taking cold medicines to combat the common cold (8), we started to focus on cold medicine-related SJS/TEN (CM-SJS/TEN) with SOC. We reported that the ocular disease was strongly associated with *HLA-A*02:06* [151 patients, 639 controls; (OR = 5.6, $p = 2.7 \times 10^{-20}$)] and significantly associated with *HLA-B*44:03* [151 patients, 639 controls; OR = 2.0, $p = 1.3 \times 10^{-3}$] (2). These HLA genotypes were not associated with cold medicine-unrelated, i.e., other medicine-related SJS/TEN with SOC (2). This suggested that the associated HLA genotypes were different and depended on the causative drug(s) (2, 4, 29). Moreover, *HLA-A*02:06* and *HLA-B*44:03* were not associated with CM-SJS/TEN without SOC (2), suggesting that different HLA genotypes were involved in the development of SJS/TEN with- and without SOC (2).

We reported that the main causative drugs for SJS/TEN with SOC in Japanese patients were cold medicines, including multi-ingredient cold medications and NSAIDs taken to combat the common cold. As we also found that acetaminophen, present in various cold medicines, was the most frequently implicated

causative drug (2, 30), we focused on acetaminophen-related SJS/TEN with SOC. Analysis of the involved HLA types revealed that *HLA-A*02:06* was strongly associated with acetaminophen-related SJS/TEN with SOC [80 patients, 113 controls; OR = 5.4, $p = 8.0 \times 10^{-7}$] (30).

Korea

Together with our Korean collaborators we investigated the HLA types (*HLA-A*02:06* and *HLA-B*44:03*) that were associated with CM-SJS/TEN with SOC in Japanese patients. We compared ours with samples from Korean patients and found that in Koreans, CM-SJS/TEN with SOC was also significantly associated with *HLA-A*02:06* (31 patients, 90 controls; OR = 3.0, $p = 0.018$), but not with *HLA-B*44:03* (3).

Our Korean collaborators suspected that NSAIDs and cold medicines were associated with SOC in Korean patients with SJS/TEN (27). They reported that allopurinol-induced SJS/TEN might not elicit serious acute or chronic complications of the ocular surface (22).

They then focused on Korean CM-SJS/TEN with SOC and investigated all of *HLA-class I (HLA-A, HLA-B, HLA-C*). In their patients they identified *HLA-A*02:06* (40 patients, 120 controls; OR = 3.0, $p = 0.0083$) and *HLA-C*03:04* (40 patients, 120 controls; OR = 3.5, $p = 0.010$) as potential positive markers for CM-SJS/TEN with SOC, and *HLA-C*03:03* (40 patients, 120 controls; OR = 0.10, $p = 0.0056$) as a possible indicator of protection against CM-SJS/TEN with SOC in the Korean population (31).

Brazil

Together with our Brazilian collaborators we investigated the HLA types (*HLA-A*02:06 and HLA-B*44:03*) that were associated with Japanese CM-SJS/TEN with SOC. Comparison of our and Brazilian samples revealed that in Brazilian CM-SJS/TEN with SOC, there was a significant association with *HLA-B*44:03* (39 patients, 134 controls; OR = 2.7, $p = 0.024$), but not with *HLA-A*02:06,* a genotype not found in all Brazilian population (3). Interestingly, focused on European ancestry of Brazilians, the association with *HLA-B*44:03* was stronger (15 patients, 62 controls; OR = 6.2, $p = 0.0037$) than in all Brazilians (3).

As the Brazilian collaborators found that 53% of their SJS/TEN with SOC patients had taken cold medicines before disease onset (24), they investigated the associated HLA types of CM-SJS/TEN with SOCs. Their studies suggested *HLA-A*66:01* as a potential marker for CM-SJS/TEN with SOCs in Brazilians (39 patients, 133 controls; OR = 24.0, $p < 0.001$) of both Pardo- (19 patients, 66 controls; OR = 12.2, $p = 0.03$) and European ancestry (16 patients, 61 controls; OR = 21.2, $p = 0.04$) and that *HLA-B*44:03* (16 patients, 61 controls; OR = 5.50, $p = 0.01$) and *HLA-C*12:03* (16 patients, 61 controls; OR = 8.79, $p = 0.008$) might be markers only in individuals of European ancestry. Moreover, they stated that *HLA-A*11:01* (39 patients, 133 controls; OR = 0.074, $p = 0.008$) might be a marker of resistance to CM-SJS/TEN with SOC (24).

Because Dipyrone was broadly used as cold medicine in Brazil, we also focused on dipyrone-related SJS/TEN with SOCs and found that *HLA-B*44:03* (carrier frequency: $p = 0.002$, Pc = 0.02, OR = 8.8; gene frequency: $p = 0.001$, Pc = 0.01, OR = 7.5) and *HLA-DQB1*04:02* (gene frequency: $p = 0.003$, Pc = 0.03, OR = 12.6) were significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of European ancestry, and that *HLA-C*05:01* (carrier frequency: $p = 0.001$, Pc = 0.01, OR = 9.4; gene frequency: $p = 0.002$, Pc = 0.02, OR = 15.0) was significantly associated with cases of dipyrone-related SJS/TEN with SOCs in the Brazilian population of mixed raced ancestry (32).

India

Together with our Indian collaborators we investigated the HLA types (*HLA-A*02:06 and HLA-B*44:03*) associated with Japanese CM-SJS/TEN with SOC.

In samples from Indian patients with CM-SJS/TEN with SOC there was a significant association with *HLA-B*44:03* (20 patients, 55 controls; OR = 12.3, $p = 1.1 \times 10^{-5}$), but not with *HLA-A*02:06* (3). Although the number of Indian patients was small, the association between Indian CM-SJS/TEN with SOC and *HLA-B*44:03* was strong and significant (3).

According to Kannabiran et al. (33), Indian ophthalmologists found it difficult to obtain a detailed history of disease onset from their SJS/TEN with SOC patients and in many patients they could not identify causative drugs. HLA analysis showed that *HLA-A*33:03* (80 patients, 50 controls; OR = 3.4, $p = 2.7 \times 10^{-3}$), *HLA-B*44:03* (80 patients, 50 controls; OR = 12.2, $p = 7.3 \times 10^{-9}$), and *HLA-C*07:01* (80 patients, 50 controls; OR = 6.5, $p = 4.4 \times 10^{-6}$) were risk alleles. *HLA-B*57:01* (80 patients, 50 controls; OR = 0.05, $p = 3.0 \times 10^{-4}$) and *HLA-C*06:02* (80 patients, 50 controls; OR = 0.1, $p = 4.0 \times 10^{-4}$) were protective alleles in the Indian population. Haplotypes comprised of *HLA-B*44:03* and *HLA-C*07:01* were strongly associated with SJS/TEN with SOC in the Indian population (80 patients, 50 controls; OR = 11.0, $p = 1.1 \times 10^{-7}$) (33).

Thailand

Together with our Thai collaborators we investigated causative drugs in their SJS/TEN with SOC patients and performed HLA analysis using Thai samples. *HLA-A*33:03* (71 patients, 159 controls; OR = 2.6, $p = 0.0028$), *HLA-B*44:03* (71 patients, 159 controls; OR = 6.0, $p < 0.0001$), and *HLA-C*07:01* (71 patients, 159 controls; OR = 4.9, $p < 0.0001$) exhibited a significant associations with SJS/TEN with SOC (25). Among 71 Thai SJS/TEN with SOC patients, 49 (69%) had a history of taking cold medications prior to SJS/TEN onset.

A focus on CM-SJS/TEN with SOC revealed that *HLA-B*44:03* (49 patients, 159 controls; OR = 7.2, $p < 0.0001$) and *HLA-C*07:01* (49 patients, 159 controls; OR = 6.1, $p < 0.0001$) were significantly associated with Thai CM-SJS/TEN with SOC. In 17 of 49 patients with CM-SJS/TEN with SOC (34.7%), a haplotype comprised of *HLA-B*44:03* and *HLA-C*07:01* was present. This was the case in only 11 of 159 controls (6.9 %) (OR = 7.1, $p = 5.5 \times 10^{-6}$), suggesting that the *HLA-B*44:03—HLA-C*07:01* haplotype was a potential risk factor for CM-SJS/TEN with SOC in the Thai population (25).

In Thailand, as in the USA and UK, cold medicines, especially acetaminophen (paracetamol), are widely-used over-the-counter

drugs. Elsewhere we reported that in Japan, acetaminophen is the most frequently included drug in various cold medicines (2, 30). Therefore, we focused on Japanese acetaminophen-related SJS/TEN with SOC and analyzed the HLA types (30). Together with our Thai collaborators we also investigated Thai patients with acetaminophen-related SJS/TEN with SOC and analyzed the HLA types. Jongkhajornpong et al. (34) reported a significant association with *HLA-A*33:03* (20 patients, 60 controls; OR = 5.4, $p = 0.0030$), *HLA-B*44:03* (20 patients, 60 controls; OR = 9.0, $p = 0.0004$), *HLA-C*07:01* (20 patients, 60 controls; OR = 9.3, $p = 0.0002$), and the *HLA-B*44:03—HLA-C*07:01* haplotype (20 patients, 60 controls; OR = 9.0, $p < 0.001$) in Thai patients with acetaminophen-related SJS/TEN with SOC, suggesting that they may have a role in the pathogenesis of SOC in acetaminophen-related SJS/TEN.

Taiwan

Our Taiwanese collaborators found that the main causative drugs in 26 Han Chinese with SJS/TEN with SOC were cold medicines; in 13 of 26 patients with SOC, cold medicines were the causative drugs, in none of 7 patients without SOC they identified cold medications as causative (26). Their findings echoed earlier studies that implicated cold medicines in the development of SOC in 80% of Japanese SJS/TEN patients (2, 35), 53% of Brazilian patients (24), and 69% of Thai patients (25).

Together with our Taiwanese collaborators we performed HLA analysis of SJS/TEN with SOC in the Han Chinese and found that *HLA-A*02:07* (26 patients, 98 controls; OR =3.2, $p = 0.049$) was associated with their development of the disease. Our focus on CM-SJS/TEN with SOC revealed that *HLA-A*02:07* (13 patients, 98 controls; OR = 5.6, $p = 0.016$) was strongly associated with the development of SOC among Han Chinese CM-SJS/TEN patients (26). Single amino acid substitutions in major histocompatibility complex (MHC) class I molecules were found to play a role in distinct peptide repertoires. For example, three *HLA-A2* subtypes, i.e., *HLA-A*02:04*, *HLA-A*02:06*, and *HLA-A*02:07*, differed by only a single amino acid residue substitution; each harbored the *HLA-A*02:01* molecule at the floor of their binding grooves. Allele-specific peptide motifs for each *HLA-A2* subtype differed substantially from the *HLA-A*02:01* motif in the dominant anchor residues (36). Although the carrier- and gene frequency of *HLA-A*02:06* in Japanese patients with CM-SJS/TEN with SOCs was significantly higher than in the control group, the frequency of *HLA-A*02:07* was similar in both groups (2). We found that the expression of *HLA-A*02:07* but not of *HLA-A*02:06* was associated with CM-SJS/TEN with SOC in the Han Chinese patients (26).

No *HLA- B*44:03* expression was detected in Han Chinese SJS/TEN patients or the controls (26), a finding compatible with earlier studies that showed that only 0.41–0.63% of the Taiwanese Han Chinese population harbored *HLA-B*44:03* (37, 38). This observation suggests a genetic diversity in the pathogenesis of SJS among different ethnic groups although, because the number of samples was small, these studies must be expanded to include more samples.

United Kingdom

Our UK collaborators found that 9 of their 28 patients with SJS/TEN with SOC (32%) had taken cold medicines (39). Together with our UK collaborators we analyzed the association of *HLA-A, HLA-B, and HLA-C* alleles with SJS/TEN in 33 patients residing in the UK (28 patients with- and 5 without SOC) and in age-matched controls. There was a statistically significant and novel negative allele association with *HLA-B*07:02* (25 patients, 15 controls; OR = 0.16, $p = 0.012$) and with *HLA-C*07:02* (25 patients, 15 controls; OR = 0.09, $p = 0.030$) in a sub-group of European ancestry SJS/TEN patients (both with and without SOC) but not in their controls. This finding identified these alleles as being protective (39). Interestingly, a focus on European ancestry patients with SJS/TEN with SOC revealed only the association with *HLA-B*07:02* (23 patients, 15 controls; OR = 0.17, $p = 0.027$), but not with *HLA-C*07:02*. When the focus was directed on European ancestry patients with CM-SJS/TEN with SOC, both associations with *HLA-B*07:02* and *HLA-C*07:02* disappeared (39). Thus, although *HLA-B*07:02* was associated with SJS/TEN with SOC in European ancestry, it may not be a biomarker for CM-SJS/TEN with SOC in that population. Because the number of samples was small, these studies must be expanded to include more samples.

DISCUSSION

A summary of our collaborative HLA analyses is shown in **Table 1**. It shows that *HLA-B*44:03* was significantly associated with CM-SJS/TEN with SOC in the Japanese (2), in Brazilians, especially European ancestry Brazilians (3, 24, 32), in Indian patients (3, 33), and in Thais (25, 34). *HLA-A*02:06* was significantly associated with CM-SJS/TEN with SOC in the Japanese (2) and in Koreans (3, 31). Ma et al. (26) suggested that *HLA-A*02:07*, differing by only a single amino acid residue substitution from *HLA-A*02:06,* might be significantly associated with CM-SJS/TEN with SOC in Taiwanese patients.

The acetaminophen-associated HLA type might be a little different between CM-SJS/TEN with SOC in Japanese- (HLA-A*02:06) (30) and Thai patients (*HLA-B*44:03—HLA-C*07:01* haplotype) (34). Moreover, the dipyrone-associated HLA types for CM-SJS/TEN with SOC in the Brazilian population were *HLA-B*44:03* and *HLA-DQB1*04:02* in European ancestry, and *HLA-C*05:01* in mixed raced ancestry (32).

We think that a common function of cold medicines such as acetaminophen, dipyrone, and NSAIDs is highly implicated in the onset of SJS/TEN with SOC (4, 23, 30, 40).

The common function of cold medicines is the suppression of prostaglandin E_2 (PGE_2) production which suppress mucocutaneous inflammation. PGE_2 acts on EP3 (PGE_2 receptor 3) in the epidermis (41) and the mucosal epithelium (42, 43) and negatively regulates mucocutaneous inflammation. We suspect that cold medicines that include acetaminophen and dipyrone could upregulate inflammatory responses by suppressing the production of PGE_2 which suppress mucocutaneous inflammation, that they augment abnormal immune responses,

TABLE 1 | Carrier frequencies of each country.

Country	Ratio of CM-SJS/TEN with SOC /SJS/TEN with SOC	CM-SJS/TEN with SOC				SJS/TEN with SOC				Acetaminophen-SJS/TEN with SOC			
		Number of cases	HLA-A	HLA-B	HLA-C	Number of cases	HLA-A	HLA-B	HLA-C	Number of cases	HLA-A	HLA-B	HLA-C
JAPAN	76.0% (76/100) (4) 68.6% (151/220) (6)	151 cases vs. 639 controls [2014 (6)]	HLA-A*02:06 OR = 5.6 $p = 2.7 \times 10^{-20}$	HLA-B*44:03 OR = 2.0 $p = 1.3 \times 10^{-3}$		40 cases vs. 113 controls [2007 (3)]	HLA-A*02:06 OR = 5.1 $p = 0.00003$ HLA-A*11:01 OR = 0.1 $p = 0.0076$			80 cases vs. 639 controls [2020 (26)]	HLA-A*02:06 OR = 6.0 $p = 4.7 \times 10^{-12}$	HLA-B*13:01 OR = 4.1 $p = 2.0 \times 10^{-3}$ HLA-B*44:03 OR = 2.4 $p = 2.1 \times 10^{-3}$	HLA-C*14:03 OR = 2.3 $p = 3.4 \times 10^{-3}$
KOREA	Not reported [NSAIDs, including cold medicine, might be associated with SOC in Korean patients with SJS/TEN (24)]	40 cases vs. 120 controls (27)	HLA-A*02:06 OR = 3.0 $p = 0.0083$		HLA-C*03:03 OR = 0.10 $p = 0.0056$ HLA-C*03:04 OR = 3.5 $p = 0.010$								
BRAZIL	52.7% (39/74) (22)	74 cases vs. 133 controls (22)	HLA-A*11:01 OR = 0.074 $p = 0.008$ HLA-A*66:01 OR = 24.0 $p < 0.001$	HLA-B*44:03 OR = 2.7 $p = 0.04$	HLA-C*12:03 OR = 5.6 $p = 0.006$								
		19 Pardo cases vs. 66 Pardo controls (22)	HLA-A*66:01 OR = 12.2 $p = 0.03$										
		16 European cases vs. 61 European controls (22)	HLA-A*66:01 OR = 21.2 $p = 0.04$	HLA-B*44:03 OR = 5.5 $p = 0.01$	HLA-C*12:03 OR = 8.8 $p = 0.008$								
INDIA	Unknown because many patients have no detail memories	20 cases vs. 55 controls(ref) (only focused on HLA-A*02:06 and B*44:03) (7)		HLA-B*44:03 OR = 12.3 $p = 1.1 \times 10^{-5}$		80 cases vs. 50 controls (28)	HLA-A*33:03 OR = 3.4 $p = 2.7 \times 10^{-3}$	HLA-B*44:03 OR = 12.2 $p = 7.3 \times 10^{-9}$ HLA-B*57:01 OR = 0.05 $p = 3.0 \times 10^{-4}$	HLA-C*06:02 OR = 0.1 $p = 4.0 \times 10^{-4}$ HLA-C*07:01 OR = 6.5 $p = 4.4 \times 10^{-6}$				
THAILAND	69.0% (49/71) (23)	49 cases vs. 159 controls (23)		HLA-B*44:03 OR = 7.2 $p < 0.0001$	HLA-C*07:01 OR = 6.1 $p < 0.0001$	71 cases vs. 159 controls (23)	HLA-A*33:03 OR = 2.6 $p = 0.0028$	HLA-B*27:04 OR = 0.065 $p = 0.0066$ HLA-B*44:03 OR = 6.0 $p < 0.0001$	HLA-C*07:01 OR = 4.9 $p < 0.0001$ HLA-C*12:02 OR = 0.11 $p = 0.0093$	20 cases vs. 60 controls (29)	HLA-A*33:03 OR = 5.4 $p = 0.0030$	HLA-B*44:03 OR = 9.0 $p = 0.0004$	HLA-C*07:01 OR = 9.3 $p = 0.0002$
TAIWAN	50.0% (13/26) (26)	13 cases vs 98 controls (26)	HLA-A*02:07 OR = 5.6 $p = 0.016$			26 cases vs. 98 controls (26)	HLA-A*02:07 OR = 3.2 $p = 0.049$						
UK (White only)	39.1% (9/23) (39)	9 cases vs 15 controls (39)		(HLA-B*07:02) Not significant $p = 0.23$		23 cases vs. 15 controls (39)		HLA-B*07:02 OR = 0.17 $p = 0.027$					

and that they elicit the induction of SJS/TEN with SOC (4, 23, 30, 40).

Besides HLA types, we investigated other SJS/TEN with SOC susceptibility genes. Our genome-wide association study revealed *IKZF1* to be a susceptibility gene for CM-SJS/TEN with SOC in Japanese-, Korean-, and Indian populations (6). It was also significantly associated with CM-SJS/TEN with SOC in Thai patients (44). Consequently, *IKZF1* may be a universal marker for CM-SJS/TEN with SOC (6, 44). Elsewhere (45) we documented that *IKZF1* regulates mucocutaneous inflammation. We reported that *IKZF1* transgenic mice developed spontaneous mucocutaneous inflammations such as ocular surface- and oral inflammation and dermatitis (45).

In the Japanese population we identified *PTGER3* as a susceptibility gene for CM-SJS/TEN with SOC (8), and we reported that *HLA-A*02:06* and *PTGER3* polymorphisms exerted additive effects in Japanese and Korean patients with CM-SJS/TEN with SOC (OR = 10.8 and 14.2, respectively) (46).

We also suggest that in addition to microbial infections and cold medicines, the combination of multiple gene polymorphisms and their interactions contributes strongly to the onset of CM-SJS/TEN with SOC. Abnormal Innate Immunity might strongly contribute the pathology of SJS/TEN with SOC (4, 23).

Despite the genetic diversity in SJS/TEN with SOC among different ethnic groups, to prevent its onset and to reduce the incidence of blindness due to SJS/TEN, efforts must continue to identify the genetic predisposition for SJS/TEN with SOC.

AUTHOR CONTRIBUTIONS

MU wrote this mini review.

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