

Letter to the Editor

Association of *IL4R* polymorphisms with Stevens-Johnson syndrome

To the Editor:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute-onset mucocutaneous diseases induced by infectious agents and/or inciting drugs.¹

Although the pathobiological mechanisms underlying the onset of SJS/TEN have not been fully established, the extreme rarity of cutaneous and ocular surface reactions to drug therapies led us to suspect individual susceptibility. In the acute stage, patients with SJS/TEN manifest vesiculobullous skin lesions, severe conjunctivitis, and persistent corneal epithelial defects. In the chronic stage, ocular surface complications such as conjunctival invasion into the cornea due to corneal epithelial stem cell deficiency persist (Fig 1, A). We observed that more than 95% of patients with SJS/TEN with ocular surface complications had lost their fingernails in the acute or subacute stage and that some continue to have transformed nails even after healing of the skin lesions (Fig 1, B). Our study focused on patients with SJS/TEN accompanied by ocular surface complications.

Previous reports suggested that SJS might have an allergic basis with drugs and infectious agents and that allergic predisposition may play a role in the development of SJS.¹ We performed polymorphism analysis of the allergy-related gene *IL4R* to examine the association between SJS/TEN and allergic predisposition.

In this study, we analyzed polymorphisms of Ile50Val (rs.1805010), Ser478Pro (rs.1805015), and Gln551Arg (rs.1801275) in the *IL4R* gene between Japanese patients with SJS/TEN and Japanese healthy volunteers. We also examined the serum IgE levels.

This study was approved by the institutional review board of Kyoto Prefectural University of Medicine, Kyoto, Japan. All experimental procedures were conducted in accordance with the principles set forth in the Helsinki Declaration. For single nucleotide polymorphism (SNP) analysis, we enrolled 70 patients with SJS/TEN; all presented with ocular surface complications. The controls were 160 healthy volunteers. All participants and volunteers were Japanese residing in Japan. The average age of the patients and controls was 45.8 ± 17.6 (SD) and 36.2 ± 11.5 (SD) years, respectively. The male:female ratio in the patient and control groups were 31:39 and 57:103, respectively. SNP analysis was performed by direct sequencing.

For total IgE measurement and antigen-specific IgE assay, we enrolled 30 patients with SJS/TEN in the chronic phase. The controls were 160 and 30 healthy volunteers, respectively. Antigen-specific IgE were detected at SRL Inc (Tokyo, Japan) by using MAST-26 (Multiple Antigen Simultaneous Test; Hitachi, Tokyo, Japan), an allergy testing system.

A summary of the case-control association study with the 3 genotyped SNPs is shown in Table I. All 3 SNPs

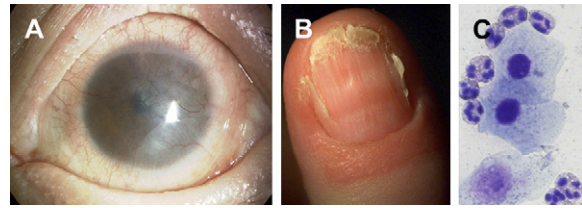


FIG 1. A, Ocular surface complications in patients with SJS/TEN in the chronic stage. B, Transformed fingernail in thumb of a 7-year-old girl, 5 months from SJS/TEN onset (subacute stage). Note the persistent nail bed inflammation. C, Discharge from the conjunctival sac of patients with SJS/TEN in the subacute stage.

were in Hardy-Weinberg equilibrium in both the patients with SJS/TEN and healthy controls ($P > .01$). Among the 3 SNPs of *IL4R*, Gln551Arg showed a significant association with allele frequency (A vs G, raw P value = .0019; corrected P value = .0057; odds ratio, 3.4) and the dominant model (A/A vs A/G + G/G, raw P value = .0025; corrected P value = 0.0075; odds ratio, 3.5). SJS/TEN was associated with Gln551Arg, shown to have no effect on IgE synthesis,² but not with Ile50Val and Ser478Pro, which are associated with IgE synthesis.^{2,3} Furthermore, in Gln551Arg polymorphisms, although Arg551 alleles were significantly increased in atopy⁴ and asthma,⁵ in patients with SJS/TEN, Gln551- but not Arg551 alleles were significantly increased. Next we investigated the relationship between serum IgE and SJS/TEN; we assayed both total and antigen-specific IgE. As shown in Table II, there was no significant difference between patients with SJS/TEN and the controls with respect to the incidence of high total serum IgE. In addition, assessment of positivity for antigen-specific IgE showed no marked difference between the 2 groups (Table III). Our results indicate that serum IgE was not associated with SJS/TEN and coincide with the finding that it was associated with Gln551Arg, which has no effect on IgE synthesis.

A strong genetic predisposition underlies the manifestation of allergic diseases.²⁻⁵ *IL4R* is representative of the candidate genes for atopy and asthma, which are biologically linked to T_H2 cytokine-driven inflammatory mechanisms.²⁻⁵

Our results show that in Japanese patients with SJS/TEN, there might be an association with polymorphisms in the *IL4R* gene. However, on the basis of our findings, we posit that SJS/TEN is different from allergic diseases such as atopy and asthma because the ratio of each allele of the polymorphisms was opposite that reported in atopy and asthma.

It has been suggested that the pathogenesis of TEN involves cytotoxic $CD8^+$ lymphocytes.⁶ Because $CD8^+$ T cells involve T_H1 cytokine-driven inflammatory mechanisms, such mechanisms may be involved in the skin inflammation seen in the acute stage of SJS/TEN. In contrast, T_H2 cytokine-driven inflammatory mechanisms

TABLE I. Genotype frequencies for *IL4R* gene SNPs and SJS/TEN susceptibility

	Control (%) (N = 160)	SJS/TEN (%) (N = 70)	Allele 1 vs allele 2	Genotype 11 vs 12+22	Genotype 11+12 vs 22
			P value (χ^2) OR (95% CI)	P value (χ^2) OR (95% CI)	P value (χ^2) OR (95% CI)
Val(G)50 Ile(A)					
11 GG	74 (46.2)	36 (51.4)	.60	.47	.99
12 GA	61 (38.1)	23 (32.9)	—	—	—
22 AA	25 (15.6)	11 (15.7)	—	—	—
Ser(T)478Pro(C)					
TT	135 (84.4)	60 (85.7)	.80	.79	—
TC	25 (15.6)	10 (14.3)	—	—	—
CC	0 (0)	0 (0)	—	—	—
Gln(A)551Arg(G)					
AA	115 (71.9)	63 (90.0)	.0019	.0025	—
AG	41 (25.6)	7 (10.0)	3.4	3.5	—
GG	4 (2.5)	0 (0)	(1.5-7.8)	(1.5-8.3)	—

TABLE II. Total serum IgE

Total IgE	SJS (N = 30)	Control (N = 160)
Normal (<173 IU/mL)	67% (20/30)	69% (111/160)
High ($\geq$ 173 IU/mL)	33% (10/30)	31% (49/160)

TABLE III. Antigen specific serum IgE (MAST-26*)

No. of positive allergens	SJS (N = 30)	Control (N = 40)
0	36.7% (11/30)	30.0% (12/40)
1	10.0% (3/30)	22.5% (9/40)
2	13.3% (4/30)	17.5% (7/40)
3	13.3% (4/30)	10.0% (4/40)
4	16.7% (5/30)	10.0% (4/40)
$\geq$ 5	10.0% (3/30)	10.0% (4/40)

*The 26 allergens in MAST-26 were house dust mite *Dermatophagoides farinae*, house dust, cat and dog epidermis, pollen from timothy, anthoxanthum odoratum, a ragweed mixture, mugwort, Japanese cedar, *Penicillium*, *Cladosporium*, *Candida*, *Alternaria*, *Aspergillus*, wheat, soy bean, rice, tuna, salmon, lobster, crab, cheddar cheese, milk, beef, chicken, and egg white.

may play a role in the inflammation seen in allergic diseases such as atopy and asthma.²⁻⁵

Ophthalmologically, the ocular surface inflammation seen in SJS/TEN is quite different from the allergic inflammation. In SJS/TEN, goblet cells in the conjunctiva are remarkably decreased or disappear,⁷ whereas in allergic diseases, their number is increased.⁸ IL4 induces the differentiation of IL4R-expressing epithelium into mucous goblet cells.⁹ We confirmed IL4R-specific mRNA expression in conjunctival epithelial cells. IL4R on the ocular surface might play an important role in the ocular surface inflammation seen in not only allergic diseases but also SJS/TEN. The discharge from the ocular surface of patients with SJS/TEN in acute or subacute stage consists primarily of neutrophils (Fig 1, C); in patients with allergic and atopic conjunctivitis, it is mainly composed of eosinophils. Thus, on the basis of both dermatologic and ophthalmologic findings, SJS/TEN is quite different from allergic diseases.

Given the association between the onset of SJS/TEN and infections,¹ we considered the possibility that there is an association between SJS/TEN and a disordered innate immune response. Therefore, we performed gene expression analysis and found that *IL4R* gene expression was different in patients with SJS/TEN and the controls; on LPS stimulation, it was downregulated in patients with SJS/TEN and slightly upregulated in the controls (data not shown). We also found that in human corneal epithelial cells, IL4R-specific mRNA was downregulated on stimulation with Polyinosine-polycytidylic acid, which mimics viral components (data not shown). Our findings suggest that IL4R might be linked with innate immunity.

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