Association of Combined IL-13/IL-4R Signaling Pathway Gene Polymorphism with Stevens-Johnson Syndrome Accompanied by Ocular Surface Complications

Mayumi Ueta, Chie Sotozono, Tsutomu Inatomi, Kentaro Kojima, Junji Hamuro, and Shigeru Kinoshita

PURPOSE. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute-onset mucocutaneous diseases induced by infectious agents or inciting drugs. The authors previously reported an association between SJS/TEN and IL-4R gene polymorphism that is essential for IL-4 and IL-13 signaling. To examine IL-4 and IL-13 gene polymorphisms and the combination of these polymorphisms with IL-4R polymorphism, the authors performed polymorphism analysis.

METHODS. In 76 Japanese SJS/TEN patients with ocular surface complications and 160 healthy controls, the authors analyzed polymorphisms of the promoter −590C/T in the IL-4 gene and of the promoter −1111C/T and Arg110Gln in the IL-13 gene and assessed Gln551Arg in the IL-4R gene. Because Arg110Gln affects serum IL-13, plasma IL-13 levels were also examined.

RESULTS. In the SJS/TEN patients, the Arg110Gln SNP of IL-13 was significantly associated with the disease, and the frequency of Arg110 alleles was significantly higher than that in the controls. Plasma IL-13 tended to be lower in SJS/TEN patients than in the controls. Analysis of the genotype pattern of IL-4R SNP Gln551Arg and IL-13 SNP Arg110Gln showed that the Gln551Gln (A/A)-Arg110Arg (G/G) genotype pattern was also associated with SJS/TEN.

CONCLUSIONS. IL-13 gene polymorphisms might be associated with SJS/TEN with ocular surface complications. The present findings suggest that SJS/TEN is different from allergic diseases such as atopy and asthma because the ratio of each allele in the IL-13 SNP Arg110Gln was the opposite of the ratio in those diseases. They also reveal that combined polymorphisms in the IL-13/IL-4R signaling pathway were associated with SJS/TEN with ocular surface complications. (Invest Ophthalmol Vis Sci. 2008;49:1809–1813) DOI:10.1167/iovs.07-1401

S t e v e n s - J o h n s o n s y n d r o m e (SJS), an acute inflammatory vesiculobullous reaction of the skin and mucous membranes first described in 1922, is commonly associated with infectious agents and inciting drugs. When there is extensive skin detachment and a poor prognosis, the condition is called toxic epidermal necrolysis (TEN). In the acute stage, SJS/TEN patients manifest vesiculobullous skin lesions, severe conjunctivitis, and persistent corneal epithelial defects because of ocular surface inflammation. In the chronic stage, ocular surface complications, such as conjunctival invasion into the cornea caused by corneal epithelial stem cell deficiency, symblepharon, ankyloblepharon, and, in some instances, keratinization of the ocular surface, persist despite healing of the skin lesions. SJS/TEN is one of the most devastating ocular surface diseases, and it leads to corneal damage and loss of vision. The reported incidence of ocular surface complications in SJS/TEN is 50% to 68%.6

We previously reported that not only environmental but also genetic factors may play important roles in an integrated etiology of SJS/TEN and that in the Japanese, HLA-A*0206 was strongly associated with SJS/TEN with ocular surface complications.7 We also documented that in Japanese patients with SJS/TEN, there was an association with toll-like receptor 3 (TLR3) polymorphisms.4 Furthermore, we found that in Japanese patients with SJS/TEN, there is an association with polymorphisms in the allergy-related IL-4R gene and that the ratio of each allele in the polymorphism was the opposite of the ratio reported in atopy and asthma.8 IL-4Rα is a component of not only the IL-4 but also the IL-13 receptor and is essential for both IL-4 and IL-13 signaling. The type 1 IL-4 receptor is composed of 2 subunits, an α subunit (IL-4Rα), which binds IL-4 and transduces its growth-promoting and transcription-activating functions, and a γ c subunit, common to several cytokine receptors, that amplifies signaling of IL-4Rα. The IL-13 receptor (IL-13Rα) is composed of the IL-4Rα chain (IL-4Rα) and the IL-13Rα1 chain (IL-13Rα1).9

Given that IL-4 is able to bind to this receptor, it is also called type 2 IL-4R.5 There exists another IL-13 binding unit, the IL-13Rα2 chain (IL-13Rα2), which acts as a decoy receptor.9

Because there is an association between SJS/TEN and IL-4R polymorphism, we speculated that there might be an association between IL-4 or IL-13 signaling and SJS/TEN. Therefore, we examined IL-4 and IL-13 gene polymorphisms and the combination of these polymorphisms with IL-4R polymorphism.

With respect to IL-4 gene polymorphisms, a variant of the promoter region of the IL-4 gene, −590C/T, has been shown to be related to asthma.10–12 Regarding IL-13 gene polymorphisms, a variant of the promoter region of the IL-13 gene, −1111C/T,13,14 and a variant of Arg110Gln were reportedly associated with asthma.15 Gln551Arg of the IL-4R gene was associated with atopy16,17 and asthma.18

Here we examined polymorphisms of the promoter −590C/T (rs.2243250) in the IL-4 gene, of −1111C/T (rs.18000925) and Arg110Gln (rs.20,541) in the IL-13 gene, and of Gln551Arg (rs.1801275) in the IL-4R gene in Japanese SJS/TEN patients with ocular surface complications and healthy volunteers. We also examined their plasma IL-13 level because...

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TABLE 1. Genotype Frequencies for Various SNPs and SJS/TEN Susceptibility

<table>
<thead>
<tr>
<th></th>
<th>Control (%), n = 160</th>
<th>SJS/TEN (%), n = 76</th>
<th>Allele 1 vs. Allele 2</th>
<th>Genotype 11 vs. 12</th>
<th>Genotype 11 vs. 22</th>
<th>Genotype 11 + 12 vs. 22</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-4 gene</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promoter-590 (rs. 2243250)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 TT</td>
<td>82 (51.3)</td>
<td>39 (51.3)</td>
<td>0.54</td>
<td>0.99</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>12 TC</td>
<td>72 (45.0)</td>
<td>30 (39.5)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>22 CC</td>
<td>6 (3.8)</td>
<td>7 (9.2)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>IL-13 gene</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Promoter-1111 (rs. 1800925)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 CC</td>
<td>101 (63.1)</td>
<td>57 (75.0)</td>
<td>0.049</td>
<td>0.07</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>12 CT</td>
<td>52 (32.5)</td>
<td>18 (23.7)</td>
<td>1.7</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>22 TT</td>
<td>7 (4.4)</td>
<td>1 (1.5)</td>
<td>(1.0–3.0)</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Arg(G)110Gln(A) (rs. 20541)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 GG</td>
<td>77 (48.1)</td>
<td>47 (61.8)</td>
<td>0.014</td>
<td>0.049</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>12 GA</td>
<td>66 (41.2)</td>
<td>27 (35.5)</td>
<td>1.8</td>
<td>1.8</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>22 AA</td>
<td>17 (10.6)</td>
<td>2 (2.6)</td>
<td>(1.1–2.8)</td>
<td>(1.0–3.0)</td>
<td>(1.0–19.6)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-4R gene</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gln(A)551Arg(G) (rs. 1801275)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 AA</td>
<td>115 (71.9)</td>
<td>69 (90.8)</td>
<td>0.0008</td>
<td>0.0011</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>12 AG</td>
<td>41 (25.6)</td>
<td>7 (9.2)</td>
<td>3.7</td>
<td>3.9</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>22 GG</td>
<td>4 (2.5)</td>
<td>0 (0)</td>
<td>(1.7–8.5)</td>
<td>(1.6–9.0)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

*P* values were determined by *χ²* testing.

**Methods**

**Patients**

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 Declaration of Helsinki. The purpose of the research and the experimental protocols were explained to all participants, and their prior written informed consent was obtained.

For single-nucleotide polymorphism (SNP) analysis, we enrolled 76 patients with SJS/TEN in the chronic or subacute phase; all presented with ocular surface complications. The diagnosis of SJS/TEN was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least two mucosal sites including the ocular surface. The controls were 160 healthy volunteers without allergic diseases such as atopic dermatitis or asthma. All participants and volunteers were Japanese residing in Japan. The average age of the patients and controls was 46.1 ± 7.3 (SD) and 36.2 ± 11.5 (SD) years, respectively. The male/female ratios in the patient and control groups were 33:43 and 57:103, respectively.

**SNP Analysis**

SNP analysis was performed by direct sequencing. PCR and sequence primers for SNPs of *IL-4* were 5’-CCAGGCTGGCACATCTGTTGAG-3’ (sense) and 5’-ACAGG TTGAGTGTGAGGAAACACT-3’ (antisense) for the −590 promoter (rs.2243250). For SNPs of *IL-13*, they were 5’-CCAT TTGCTGATAGGTTGAG-3’ (sense) and 5’-GGCTGAGGTCTAAGCTAGTTGAGGAGGATCACCC-3’ (antisense) for Arg110Gln (rs.20,541), and 5’-ATGTTCTGGTTGTGAGGTTTACCAAC-3’ (antisense) for the promoter-1111 (rs.1800925). For Gln551Arg (rs.1801275) of *IL-4R* SNPs, they were 5’-AGCTTCAAGAATCTGTTGAG-3’ (sense) and 5’-CCAAACCCACATTTTCTC-3’ (antisense). Genomic DNA was isolated from peripheral blood by Dr. T. Shiga (Shiga University of Medical Science, Shiga, Japan) and Dr. M. Ohashi (Tokyo Metropolitan Central Hospital, Tokyo, Japan) using a commercial PCR machine (GeneAmp; Applied Biosystems, Foster City, CA). The PCR products were reacted (BigDye Terminator v3.1; Applied Biosystems), and sequence reactions were resolved on a genetic analyzer (ABI PRISM 3100; Applied Biosystems).

**Statistical Methods Used for SNP Analysis**

Alleles were counted manually. Each allele was assessed as an independent variable, and separate *P* values were calculated for each polymorphism. *P* < 0.05 was regarded as significant. In addition, *P* was corrected for the number of alleles tested in each gene (Bonferroni method).

**Measurement of Plasma IL-13 Levels**

For the measurement of plasma IL-13 levels, we enrolled 29 patients with SJS/TEN in the chronic or subacute phase; all presented with ocular surface complications (Arg110/Arg110, n = 14; Arg110/Gln110, n = 14; Gln110/Gln110, n = 10). All patients and volunteers were Japanese residing in Japan. The average age of the patients and controls was 46.1 ± 7.3 (SD) and 36.2 ± 11.5 (SD) years, respectively. The male/female ratios in the patient and control groups were 33:43 and 57:103, respectively.

**Results**

A summary of our case-control association study with the four genotyped SNPs is shown in Table 1. All four SNPs were in Hardy-Weinberg equilibrium in the SJS/TEN patients and the healthy controls (*P > 0.01*). In the promoter −590C/T SNP of the *IL-4* gene related to higher IgE levels, there was no significant association. In the promoter −1111C/T SNP of the *IL-13* gene related to asthma, there was a weak association with allele frequency (*C* vs. *T*, raw *P* = 0.049, corrected *P* = 0.099; odds ratio = 1.7); correction of the *P* value for the number of alleles detected (n = 2) rendered the result not significant. Gln110Arg SNPs of *IL-13* exhibited a significant association with allele frequency (*G* vs. *A*, raw *P* = 0.014, 1 minute on a commercial PCR machine (GeneAmp; Applied Biosystems, Foster City, CA). The PCR products were reacted (BigDye Terminator v3.1; Applied Biosystems), and sequence reactions were resolved on a genetic analyzer (ABI PRISM 3100; Applied Biosystems).

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corrected \( P = 0.028 \); odds ratio = 1.8) even when we corrected \( P \) for the number of alleles detected of \( IL13 \) SNPs (\( n = 2 \)). They also exhibited a weak association with the dominant model (G/G vs. G/A, raw \( P = 0.049 \), corrected \( P = 0.097 \); odds ratio = 1.8) and the recessive model (G/G + G/A vs. A/A, raw \( P = 0.035 \), corrected \( P = 0.07 \); odds ratio = 4.4); correction of the \( P \) value for the number of alleles detected (\( n = 2 \)) rendered the result not significant. These findings contrast with those of Heinzmann et al.,15 who reported that Gln110 was significantly increased in human asthma. We detected a significant increase in Arg110 in our SJS/TEN patients.

The Gln551Arg SNP of the \( IL13 \) gene showed a significant association with allele frequency (A vs. G, raw \( P = 0.0008 \); odds ratio = 3.7) and the dominant model (A/A vs. A/G + G/G, raw \( P = 0.0011 \); odds ratio = 3.9); these findings coincide with those we reported previously.14

We also studied the plasma IL-13 levels in our SJS/TEN patients because these levels were reportedly higher in patients with Gln110.19 We compared plasma IL-13 levels in 28 SJS/TEN patients because these levels were reportedly higher in patients with Arg110Arg (Fig. 1A). Plasma IL-13 levels tended to be lower in patients than in controls. However, the difference was not statistically significant. Evaluation was with Student's \( t \)-test using a spreadsheet program.

**DISCUSSION**

Arg110Gln, which affects the plasma IL-13 level; in SJS/TEN there is a significant increase in the Arg110 allele, which might lead to lower serum IL-13 levels than the Gln110 allele.

We also analyzed the genotype pattern of \( IL4R \) SNP Arg551Gln and \( IL13 \) SNP Arg110Gln. We found that the Gln551Gln(A/A)-Arg110Gln(A/G) genotype pattern also associated with SJS/TEN in Japanese patients (\( \chi^2 \) test; \( P = 0.0006 \), OR = 2.6, 95% CI, 1.5–4.6; Table 2). In more detail, 69 of 76 (90.8%) SJS/TEN patients and 115 of 160 (71.9%) controls had \( IL4R \) Gln551Gln (Table 1), and 44 of 76 (57.9%) SJS/TEN patients and 55 of 160 (34.4%) controls had the genotype pattern Gln551Gln(A/A)-Arg110Gln(G/G) of the \( IL13 \) type 1 pattern; Table 2). Therefore, 44 of 69 SJS/TEN patients with \( IL4R \) Gln551Gln (63.8%) had the type 1 pattern, whereas only 55 of 115 controls with \( IL4R \) Gln551Gln (47.8%) had the type 1 pattern. This result shows that SJS/TEN patients with \( IL4R \) Gln551Gln have \( IL13 \) Arg110Arg more frequently than controls with \( IL4R \) Gln551Gln; there was a significant difference between SJS/TEN and controls (\( \chi^2 \) test; \( P = 0.036 \), OR = 1.9; 95% CI, 1.0–3.5). Thus, we suggest a combined effect exists between \( IL4R \) and \( IL13 \) polymorphisms.

**Table 2.** Pattern Structures and Frequencies of \( IL13 \) SNP Arg110Gln and \( IL4R \) SNP Arg551Gln

<table>
<thead>
<tr>
<th>Pattern Type</th>
<th>( IL4R ) SNP</th>
<th>( IL13 ) SNP</th>
<th>Control (%)</th>
<th>SJS/TE (%)</th>
<th>( P )</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A/A</td>
<td>G/G</td>
<td>55/160 (34.4)</td>
<td>44/76 (57.9)</td>
<td>0.0006</td>
<td>2.6 (1.5–4.6)</td>
</tr>
<tr>
<td>2</td>
<td>A/A</td>
<td>A/G</td>
<td>48/160 (30.0)</td>
<td>25/76 (30.3)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>A/G</td>
<td>A/G</td>
<td>20/160 (12.5)</td>
<td>3/76 (3.9)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>A/G</td>
<td>G/G</td>
<td>16/160 (10.0)</td>
<td>4/76 (5.3)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>A/A</td>
<td>A/A</td>
<td>12/160 (7.5 )</td>
<td>2/76 (2.6)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>G/G</td>
<td>A/G</td>
<td>2/160 (1.3)</td>
<td>0/76 (0.0)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>G/G</td>
<td>A/G</td>
<td>2/160 (1.3)</td>
<td>0/76 (0.0)</td>
<td>NS</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>A/G</td>
<td>A/A</td>
<td>2/160 (1.3)</td>
<td>0/76 (0.0)</td>
<td>NS</td>
<td>—</td>
</tr>
</tbody>
</table>

* \( P \) values were determined by \( \chi^2 \) testing.
plasma IL-13 level.\textsuperscript{13} In SJS/TEN, Arg110 alleles are significantly increased, but in atopy and asthma, Gln110 alleles are significantly increased.\textsuperscript{15} Plasma IL-13 tended to be lower in our SJS/TEN patients with ocular surface complications than in the controls because plasma IL-13 was lower in the presence of Arg110Arg than in the presence of Gln110Arg.\textsuperscript{16} Although our results suggest that in Japanese SJS/TEN patients with ocular surface complications there might be an association with polymorphisms in the allergy-related IL-13 genes, SJS/TEN is different from allergic diseases such as atopy and asthma because the ratio of each allele of the IL-13 SNP Arg110Gln was opposite the ratio in atopy and asthma. In SJS/TEN, Arg110 rather than Gln110 alleles (which are significantly increased in asthma)\textsuperscript{15} showed a significant increase. Arima et al.\textsuperscript{17} have reported that the Gln110 variant of Gln110Arg decreased the affinity with IL-13R\alpha. The strong difference between serum IgE and SJS/TEN also showed that there was no significant difference between SJS/TEN patients and controls with respect to the incidence of high total serum IgE.\textsuperscript{8}

In Arg110Gln of IL-13 polymorphisms and Gln551Arg of IL-4R polymorphisms, the ratio of each allele was the inverse of the ratio reported for atopy and asthma; therefore, SJS/TEN appears to be different from those allergic diseases. Moreover, combined polymorphisms in the IL-13/IL-4R signaling pathway are also associated with SJS/TEN patients; we document that Gln551Gln(A/A) of the IL-4R and Arg110Arg(G/G) of the IL-13 genotype pattern were also associated with SJS/TEN with ocular surface complications.

In patients with acute-phase SJS/TEN, dermatologists have examined IL-13 levels in serum or skin lesions and reported that the expression level of IL-13 is upregulated in patients with SJS/TEN, whereas Arg551 alleles were significantly increased in atopy and asthma. Our earlier study on the relationship between serum IgE and SJS/TEN also showed that there was no significant difference between SJS/TEN patients and controls with respect to the incidence of high total serum IgE.\textsuperscript{8}

In patients with acute-phase SJS/TEN, dermatologists have examined IL-13 levels in serum or skin lesions and reported that the expression level of IL-13 is upregulated in patients with SJS/TEN.\textsuperscript{15} Given that CDB\textsuperscript{T} cells involve Th1 cytokine-driven inflammatory mechanisms, such mechanisms may be involved in the skin inflammation seen in the acute stage of SJS/TEN. In contrast, Th2 cytokine-driven inflammatory mechanisms may play a role in the inflammation seen in allergic diseases such as atopy and asthma.\textsuperscript{22} Thus, genetic alterations in the IL-13/IL-4R signaling pathway may regulate Th1 or Th2 cytokine-driven inflammatory mechanisms.

We suggested elsewhere that IL-4R might be linked to innate immunity.\textsuperscript{8} The innate immune system may constitute a link between the environment and the adaptive immune system. We are continuing to examine the pathophysiology of SJS/TEN with ocular surface complications.

Acknowledgments

The authors thank Chikako Mochida for technical assistance.

References


