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[III]

研究成果の刊行物・別刷

Original article

Association between prostaglandin E receptor 3 polymorphisms and Stevens-Johnson syndrome identified by means of a genome-wide association study

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Background: Stevens-Johnson syndrome (SJS) and its severe variant, toxic epidermal necrolysis (TEN), are acute inflammatory vesiculobullous reactions of the skin and mucosa. They often affect the ocular surface and can result in permanent visual dysfunction.

Objectives: We sought to discover genetic markers for SJS/TEN susceptibility.

Methods: We performed a genome-wide association study with 60 patients and 300 control subjects. We applied stringent filter and visual assessments for selecting single nucleotide polymorphisms (SNPs) and a high false discovery rate threshold. We fine-mapped the region where a candidate SNP was found and confirmed the results by means of sequencing. We evaluated the function of agonist-activated prostaglandin E receptor 3 (EP3), the gene for which contained several SNPs, in regulating cytokine production in human conjunctival epithelial (CE) cells. The expression levels of EP3 in the CE cells from patients and control subjects were also compared.

Results: We identified 3 SNPs that passed the false discovery rate threshold. One (rs17131450) was close to the *EP3* gene. Therefore we analyzed the *EP3* region in detail and identified 5 other SNPs. We confirmed the association between SJS/TEN and all 6 SNPs. Activated EP3 was expressed in control CE cells, and it suppressed polyI:C-stimulated cytokine production, suggesting that EP3 might help prevent ocular surface inflammation. Concordantly, the EP3 levels were much lower in the CE cells of the patients than in those of the control subjects.

Conclusion: We demonstrated, using both genetic and functional analyses, that *EP3* could be a key player in the pathogenesis of SJS/TEN accompanied by ocular complications. (J Allergy Clin Immunol 2010;■■■:■■■-■■■.)

Key words: *Prostaglandin E receptor 3, Stevens-Johnson syndrome, toxic epidermal necrolysis, genome-wide association study, single nucleotide polymorphism*

Stevens-Johnson syndrome (SJS) and its severe variant, toxic epidermal necrolysis (TEN), are acute-onset mucocutaneous diseases (Fig 1, *A*) induced by infectious agents or an adverse reaction to a drug.[1-8] Although the annual incidences of SJS and TEN are very low, 0.4 to 1 and 1 to 6 cases per million persons, respectively,[8] they have a significant public health effect because the mortality rate is high (ie, 3% and 27%, respectively). Healthy children and adults can suddenly get these diseases, and any drug approved worldwide is a candidate instigator.[3,9-12] Associations between HLA type and drug-induced severe cutaneous adverse reactions, including SJS and TEN, have been reported.[13-21]

Patients with ocular involvement (50% to 68%)[8,11] exhibit severe conjunctivitis, and corneal epithelial defects often persist because of ocular surface inflammation.[4,22] Even after the skin lesions have healed, ocular surface complications, such as conjunctival invasion of the cornea, severe dryness of the eye, and, in some instances, keratinization of the ocular surface, can persist (Fig 1, *B*).[23] Representative causative drugs of SJS/TEN with ocular involvement are cold remedies, antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs).[4,5,7,23] In this study we focused exclusively on patients with SJS/TEN with ocular involvement. Hereafter, "SJS/TEN" denotes SJS/TEN accompanied by ocular complications.

Although the pathobiological mechanisms underlying the onset of SJS/TEN have not been fully established, the extreme rarity of the cutaneous, mucosal, and ocular surface reactions to drug therapies led us to suspect individual susceptibility. Previously, we performed a single nucleotide polymorphism (SNP) association analysis of candidate genes to investigate whether a genetic predisposition for SJS/TEN exists and to identify culpable polymorphisms. We found SJS/TEN-associated polymorphisms in the genes encoding Toll-like receptor 3 (TLR3),[5-7] IL-4 receptor,[24,25] and Fas ligand[26] in ethnic Japanese patients. We also showed that in Japanese patients HLA-A*0206 is strongly associated with the disease.[27,28] Therefore it is quite obvious that not

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Abbreviations used

BRLMM: Bayesian Robust Linear Model with a Mahalanobis distance classifier
CE: Conjunctival epithelium
EP3: Prostaglandin E receptor 3
FDR: False discovery rate
GAPDH: Glyceradlehyde-3-phosphate dehydrogenase
GWAS: Genome-wide association study
HapMap-CHB: HapMap Han Chinese
HapMap-JPT: HapMap Japanese
LD: Linkage disequilibrium
MAF: Minor allele frequency
NSAID: Nonsteroidal anti-inflammatory drug
PGE_2: Prostaglandin E_2
PHCjE: Primary human cultivated conjunctival epithelial
QC: Quality control
SJS: Stevens-Johnson syndrome
SNP: Single nucleotide polymorphism
TEN: Toxic epidermal necrolysis
TLR3: Toll-like receptor 3

only environmental but also genetic factors contribute to the cause of SJS/TEN.

To elucidate the pathophysiology of SJS/TEN in more detail, in the current study we performed a genome-wide association study (GWAS) and analyzed more than 300,000 SNPs. This method permits the identification of genetic loci and genes associated with complex human traits without bias or *a priori* knowledge of the function or involvement of any gene in the disease pathway. For example, by using this strategy, our group identified SNPs in 3 different genomic loci that have modest associations with primary open-angle glaucoma.[29] In the GWAS we found 3 SNPs that were significantly associated with SJS/TEN.

Using a fine-mapping approach, we found several SNPs in the prostaglandin E receptor 3 *(EP3)* gene that were significantly associated with SJS/TEN. Supporting the genetic association of these polymorphisms with the disease, we also found that EP3 suppressed the production of cytokines induced by polyI:C stimulation and that EP3 expression was greatly reduced compared with that seen in control subjects in the conjunctival epithelium (CE) of patients with SJS/TEN, suggesting EP3 contributes functionally to the pathogenesis of SJS/TEN.

METHODS

Patients

This study was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine. All experimental procedures were conducted in accordance with the principles set forth in the Declaration of Helsinki. The purpose of the research and experimental protocols was explained to all the participants, and their prior written informed consent was obtained.

The diagnoses of SJS and TEN were based on a confirmed history of acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites, including the ocular surface. In the patients with SJS/TEN receiving a diagnosis in the acute stage at our hospital, a histological diagnosis using skin biopsy was also performed (Fig 1, *A*).[30-32] The detailed information of the patients with SJS/TEN and the control subjects who were analyzed is shown in the Methods section and Table E1 of this article's Online Repository at www.jacionline.org.

GWAS and subsequent fine-mapping of SNPs to the *EP3* region

To identify SNPs associated with SJS/TEN by means of a GWAS, we used an Affymetrix GeneChip Mapping 500K Array Set (Affymetrix, Santa Clara, Calif), according to the manufacturer's instructions (see the Methods section in this article's Online Repository).[29]

Fine-mapping analysis of the *EP3* region was performed with the iSelect Custom Infinium Genotyping system (iSelect; Illumina, Inc, San Diego, Calif), according to the manufacturer's instructions (see the Methods section in this article's Online Repository).[29]

SNP confirmation by means of direct sequencing

The 6 SJS/TEN-associated SNPs that showed significant associations ($P < .01$) in the fine-mapping analysis were confirmed by means of sequencing, as described previously (see the Methods section in this article's Online Repository).[7,24-26] The primers for both PCR and sequencing are shown in Table E2 in this article's Online Repository at www.jacionline.org. Each allele was assessed as an independent variable, and separate *P* values were calculated for each SNP. *P* values of less than .05 were regarded as statistically significant. In addition, the *P* values were corrected according to the number of samples tested (Bonferroni correction).

Human conjunctival tissues and primary human cultivated CE cells

For RT-PCR of the human CE, we used human CE cells obtained from healthy volunteers by means of impression cytology. The primary human cultivated conjunctival epithelial (PHCjE) cells were obtained from conjunctival tissue acquired during surgical intervention to treat conjunctivochalasis.

For immunohistochemistry, human conjunctival tissues were prepared from samples obtained during surgeries to reconstruct the ocular surface as treatment for various ocular surface diseases, including SJS and pterygium. As the control, we used the nearly normal conjunctival tissues obtained during surgery for conjunctivochalasis, a disease in which the conjunctiva relaxes because of aging, resulting in a foreign body sensation on the ocular surface.

For ELISAs, PHCjE cells were cultured as previously described (see the Methods section in this article's Online Repository at www.jacionline.org).[33]

RT-PCR

RT-PCR was performed, as previously described.[34,35] Amplification was performed with DNA polymerase (Takara, Shiga, Japan) for 40 cycles at 94°C for 1 minute, 58°C for 1 minute, and 72°C for 1 minute for human *EP3* (GeneAmp; Applied Biosystems, Foster City, Calif). The primers for human *EP3* and human glyceradlehyde-3-phosphate dehydrogenase *(GAPDH)* were, respectively: forward 5′- CGT GTA CCT GTC CAA GCA GCG TTG GGA GCA -3′ and reverse 5′- CCG TGT GTG TCT TGC AGT GCT CAA CTG ATG -3′; forward 5′- CCA TCA CCA TCT TCC AGG AG-3′ and (reverse) 5′- CCT GCT TCA CCA CCT TCT TG-3′.

Immunohistochemistry

The human conjunctival tissues were embedded in OCT compound (Sakura Finetek, Torrance, Calif) and flash-frozen in liquid nitrogen. Sections 6 μm thick were cut and fixed in 100% acetone at 4°C for 10 minutes. Immunohistochemistry was performed as previously described (see the Methods section in this article's Online Repository).[35]

ELISA

The amounts of CXCL11, CCL20, IL-6, and IL-8 released into the culture supernatant were determined by means of ELISA with the Human CXCL11, CCL20 DuoSet (R&D Systems, Inc, Minneapolis, Minn) or the OptEIATM IL-6 and IL-8 set (BD PharMingen, San Diego, Calif), respectively, according to the manufacturer's instructions.

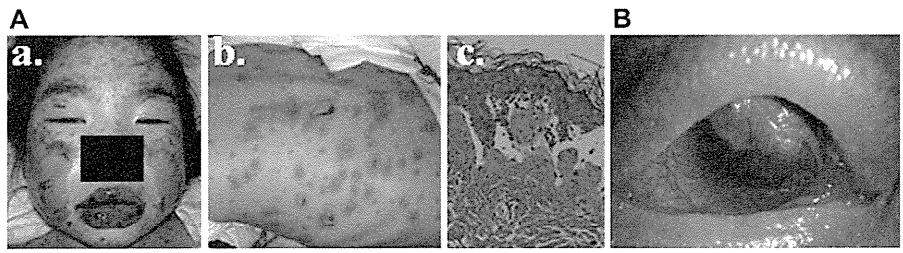

FIG 1. **A**, Skin eruptions accompanying the mucocutaneous illness of patients with SJS/TEN at the acute stage. *a*, Face with vesiculobullous lesions, conjunctivitis, and swollen crusted lips. *b*, Vesiculobullous lesions of the skin. *c*, Skin biopsy specimens of the erythematous macules showing necrotic keratinocytes and liquefaction degeneration. **B**, Ocular surface complications of patients with SJS/TEN. Conjunctival invasion results in severe vision loss.

Quantitative RT-PCR

Quantitative RT-PCR analyses for *CXCL11*, *CCL20*, and *IL6* mRNAs were performed on an ABI-prism 7700 (Applied Biosystems), as previously reported.[33-35] The primers and probes for human *CXCL11*, *CCL20*, *IL6*, and *GAPDH* were from Applied Biosystems.

Data analysis

To manage the genotype data and perform statistical analysis, we used a laboratory information management system, LaboServer (World Fusion, Tokyo, Japan). For the genotype frequency comparisons of SNPs between cases and control subjects, we used Hardy-Weinberg equilibrium analysis and the χ^2 test.

For the ELISA and quantitative RT-PCR analysis, data were expressed as mean ± SEM and were evaluated by using the Student *t* test.

RESULTS

GWAS

After genotyping 500,568 SNPs from 60 patients with SJS/TEN (cases) and 300 control subjects, we selected 313,924 SNPs using the stringent criteria chosen for our quality control (QC) filter (see the Methods section in this article's Online Repository). To identify SNPs associated with SJS/TEN, we compared the genotype frequency of each SNP between cases and control subjects. Twenty-five SNPs passed the threshold for the false discovery rate (FDR; 0.05; see Fig E1 in this article's Online Repository at www.jacionline.org). We then visually checked the 2-dimensional cluster plots of these SNPs (see the Methods section in this article's Online Repository at www.jacionline.org), and 3 of them passed our QC test (Table I). In subsequent experiments we focused on an SNP (rs17131450) that mapped close to the *EP3* gene, which is located in the 1p31 region of the human genome (Fig 2, *A*, and Table I) because the other 2 SNPs were from the "gene desert" region (see Figs E2-E5 in this article's Online Repository at www.jacionline.org).

Fine-mapping analysis of the *EP3* region

Based on the GWAS result, we performed a fine-mapping analysis of the *EP3* region using 75 cases and 448 control subjects (see Fig E6 in this article's Online Repository). We generated a custom DNA array (see the Methods section in this article's Online Repository) to analyze the SNPs in and near *EP3* through the 2 major linkage disequilibrium (LD) blocks of the HapMap Japanese (HapMap-JPT) plus HapMap Han Chinese (HapMap-CHB) populations residing within the region (Fig 2, *A*, *green bar*). We compared the genotype frequencies of 86 SNPs selected by our stringent QC filter between the cases and control subjects (see the Methods section in this article's Online Repository). The SNP (rs17131450) that showed a significant association with SJS/TEN in the GWAS also showed a significant association ($P < .01$) in the fine-mapping analysis. We also identified 5 other significantly associated ($P < .01$) SNPs in *EP3* (rs5702, rs1325949, rs7543182, rs7555874, and rs4147114; Fig 2, *A* and *C*). All of the SNPs, except rs4147114, were in Hardy-Weinberg equilibrium ($P > .05$) in the control samples. We rechecked the 2-dimensional cluster plot for rs4147114 precisely and confirmed that the distribution of the cluster was normal. One of the SNPs in *EP3* was in an exon as a silent SNP, and the other 4 were in introns (Fig 2, *C*).

TABLE I. SJS/TEN-associated SNPs obtained from the initial GWAS

SNP ID	Chromosome	SNP type	MAF	HWE in control*	Call rate†	*P* value (−log P)‡
rs1325975	6	Intergenic	0.11	0.12	0.99	5.83
rs17131450	1	Intergenic	0.09	0.11	1.00	5.77
rs11238074	11	Intergenic	0.12	0.04	0.99	5.62

**P* value for the deviation from Hardy-Weinberg equilibrium.
†Call rate per SNP in cases plus control subjects.
‡*P* value for genotype frequency comparison between cases and control subjects.

Sequencing analysis of the SJS/TEN-associated SNPs

Finally, we assessed the association of the 6 SNPs obtained from the fine-mapping analysis by sequencing samples from 100 cases and 160 control subjects. A summary of the case-control analysis based on the sequence data is shown in Table II. The association of all 6 SNPs was statistically significant, even with the Bonferroni correction ($P < .0083$). in the dominant model (Table II and Fig 2, *B*). All were in Hardy-Weinberg equilibrium ($P > .001$) in both the case and control samples. Four of the 5 SNPs in *EP3* (rs5702, rs1325949, rs7543182, and rs7555874) showed a strong LD with each other (average $D' > 0.9$, $r^2 > 0.7$; Fig 2, *B*). We identified 2 major haplotypes (types 1 and 2) of these 4 SNPs (Table III), and we also observed a significant association with SJS/TEN in various combinations of haplotypes. Consequently, from the results of the initial GWAS to those of direct sequencing, we successfully identified 6 SNPs associated with SJS/TEN, 5 of which were located within the *EP3* gene.

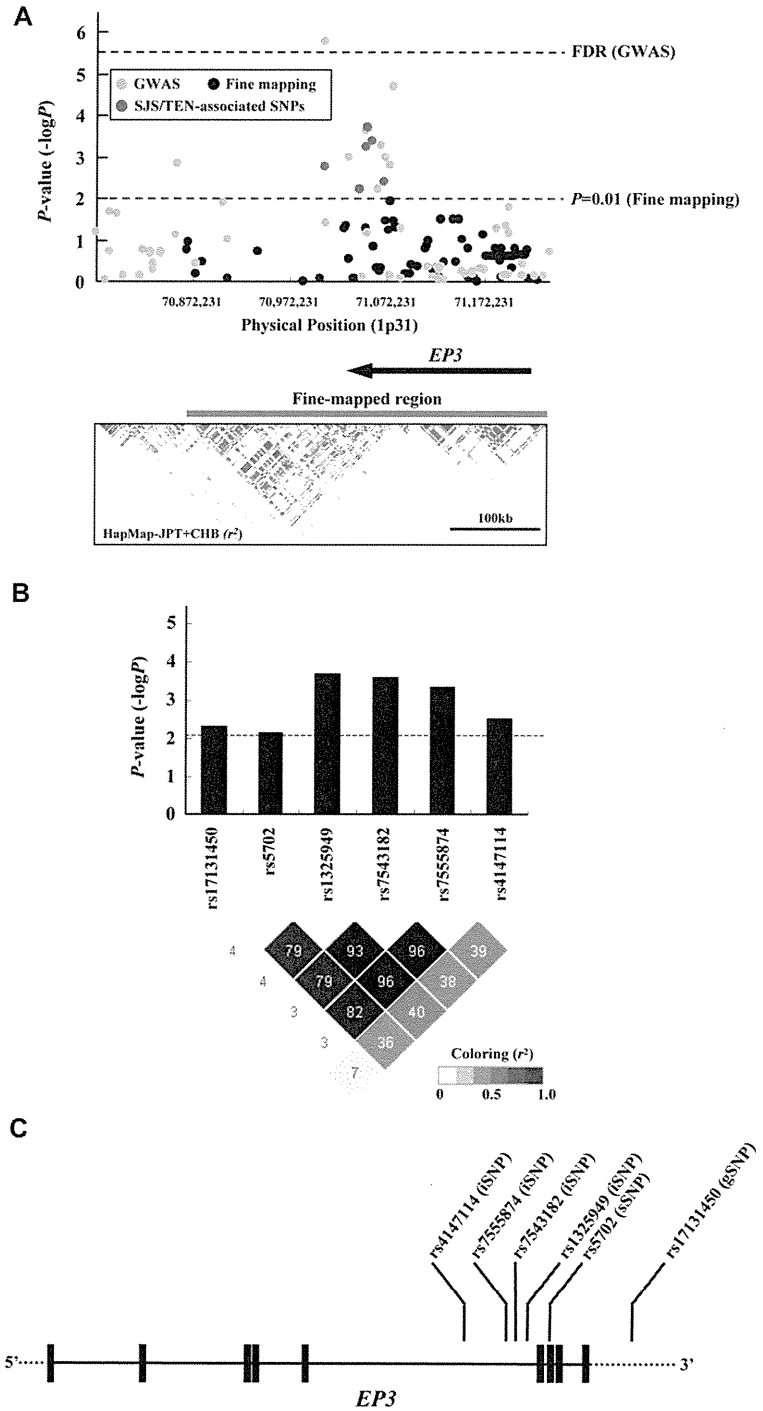

FIG 2. Association of SNPs in the *EP3* gene with SJS/TEN. **A**, Distribution of *P* values from the GWAS and fine-mapping analysis *(horizontal green bar)* of the *EP3* region. We obtained 6 significant SNPs with *P* values of less than .01 (genotype frequency comparison; *red dots*). The *P* values were plotted against the physical position of the 1p31 region and are shown for the GWAS *(gray dots)* and fine-mapping analysis *(black dots)*. *Horizontal lines*, FDR threshold for the GWAS, which was exceeded by rs17131450 (FDR; $P = 4.0 \times 10^{-6}$, *black dotted line*), and the threshold for the fine-mapping analysis ($P = .01$, *blue dotted line*). *Horizontal arrow*, Orientation of *EP3* gene transcription. The LD block of the HapMap-JPT plus HapMap-CHB populations was obtained from the USCS Genome Browser (http://genome.ucsc.edu/; National Center for Biotechnology Information build 35). **B**, Sequencing analysis of the SNPs associated with SJS/TEN. The *P* value of a dominant model for each SNP was calculated (see also Table II). *Dotted line*, Significance threshold for the Bonferroni correction. Pairwise r^2 plots among the SNPs were generated with Haploview software (http://www.broadinstitute.org/haploview/haploview). **C**, Schematic representation of the *EP3* gene structure and the location of the SNPs associated with SJS/TEN. Note that the direction of transcription is the reverse of that shown in Fig 2, *A*.

TABLE II. Genotype frequencies and association results for SJS/TEN-associated SNPs

SNP	Position (chromosome 1)	Genotypes	Frequency of genotypes (%) Control subjects (n = 160)	Patients with SJS/TEN (n = 100)	Association results Allele 1 vs allele 2 P value,* OR (95% CI)	Genotype 11 vs 12+22 P value,* OR (95% CI)	Genotype 11+12 vs 22 P value,* OR (95% CI)
rs17131450	71,296,002	11 CC	141 (88.1)	75 (75.0)	.00056, 0.36 (0.2-0.7)	.00600, 0.40 (0.2-0.8)	.0092, 0.10 (0.01-0.7)
		12 CT	18 (11.3)	19 (19.0)			
		22 TT	1 (0.6)	6 (6.0)			
rs5702	71,331,430	11 CC	80 (50.0)	67 (67.0)	.0300, 1.6 (1.0-2.4)	.00710, 2.0 (1.2-3.4)	.97, ND (ND)
		12 CT	67 (41.9)	25 (25.0)			
		22 TT	13 (8.1)	8 (8.0)			
rs1325949	71,337,193	11 AA	76 (47.5)	71 (71.0)	.0014, 2.0 (1.3-3.1)	.00020, 2.7 (1.6-4.6)	.61, ND (ND)
		12 AG	70 (43.8)	22 (22.0)			
		22 GG	14 (8.8)	7 (7.0)			
rs7543182	71,339,973	11 GG	80 (50.0)	73 (73.0)	.0023, 2.0 (1.3-3.1)	.00025, 2.7 (1.6-4.6)	.88, ND (ND)
		12 GT	68 (42.5)	20 (20.0)			
		22 TT	12 (7.5)	7 (7.0)			
rs7555874	71,343,960	11 GG	80 (50.0)	72 (72.0)	.0037, 1.9 (1.2-2.9)	.00046, 2.6 (1.5-4.4)	.88, ND (ND)
		12 GA	68 (42.5)	21 (21.0)			
		22 AA	12 (7.5)	7 (7.0)			
rs4147114	71,356,665	11 CC	42 (26.3)	44 (44.0)	.0033, 1.7 (1.2-2.5)	.0031, 2.2 (1.3-3.7)	.09, ND (ND)
		12 CG	82 (51.3)	42 (42.0)			
		22 GG	36 (22.5)	14 (14.0)			

ND, Not determined; OR, odds ratio.
**P* value for allele or genotype frequency comparison between cases and control subjects by using the χ^2 test.

TABLE III. Haplotypes of the SNPs in *EP3* associated with SJS/TEN

Types	SNPs rs5702	rs1325949	rs7543182	rs7555874	Frequency (%) Control subjects (n = 160)*	Patients with SJS/TEN (n = 100)*
1	C/C	A/A	G/G	G/G	46.3	67.0
2	C/T	A/G	G/T	G/A	40.0	19.0
3	T/T	G/G	T/T	A/A	7.5	7.0
4	Other combinations				6.3	8.0

*Number of subjects analyzed.

EP3 mRNA and protein expression in human ocular surface epithelium

We previously reported that EP3 is constitutively expressed in murine CE.[35] Given the association between SNPs in *EP3* and SJS/TEN and the murine expression pattern, we examined the expression of *EP3* in human CE. First, we used RT-PCR to examine the expression of *EP3* mRNA and obtained PCR products of the expected length (622 bp) from the human CE samples (Fig 3, *A, a*). PCR products were isolated and sequenced to confirm their identity. The sequences were identical to that of the human *EP3* cDNA (data not shown).

Immunohistochemistry of control human conjunctival tissue (using conjunctival tissues from a patient with conjunctivochalasis as a normal conjunctival sample) showed obvious EP3 protein expression in the CE (Fig 3, *A, b*).

Suppression of cytokine production by an EP3 agonist

We previously reported that prostaglandin E_2 (PGE_2) is a ligand for EP3 in murine CE and that it downregulates the progression of murine experimental allergic conjunctivitis.[35] We also reported that *TLR3* polymorphisms are associated with SJS/TEN in ethnic Japanese subjects,[7] that the human ocular surface epithelium expresses TLR3, and that cytokine production is upregulated by polyI:C, a TLR3 ligand.[6,34] On the basis of these findings, we examined the function of EP3 in polyI:C-stimulated PHCjE cells using an EP3 agonist, ONO-AE248. PHCjE cells that were untreated or pretreated with 10 μg/mL ONO-AE248 were incubated for 24 hours with 10 μg/mL polyI:C. As early as 24 hours after adding polyI:C, we found high levels of CXCL11, CCL20, IL-6, and IL-8 in the supernatants from the polyI:C-treated, but ONO-AE248-untreated, PHCjE cultures (Fig 3, *B, a*). Cultures pretreated with ONO-AE248 produced significantly lower levels of CXCL11, CCL20, and IL-6, but the level of IL-8 was not affected (Fig 3, *B, a*). The mRNA levels for *CXCL11*, *CCL20*, and *IL6* were also significantly less in the PHCjE cultures pretreated with ONO-AE248 compared with those seen in the untreated cultures (Fig 3, *B, b*).

Taken together, these results show that cytokine production by the CE in response to polyI:C stimulation can be suppressed through the activation of EP3.

Reduced EP3 expression in the CE of patients with SJS/TEN

Next we examined the expression of EP3 in the CE of patients with SJS/TEN by means of immunohistochemistry. Unlike in the

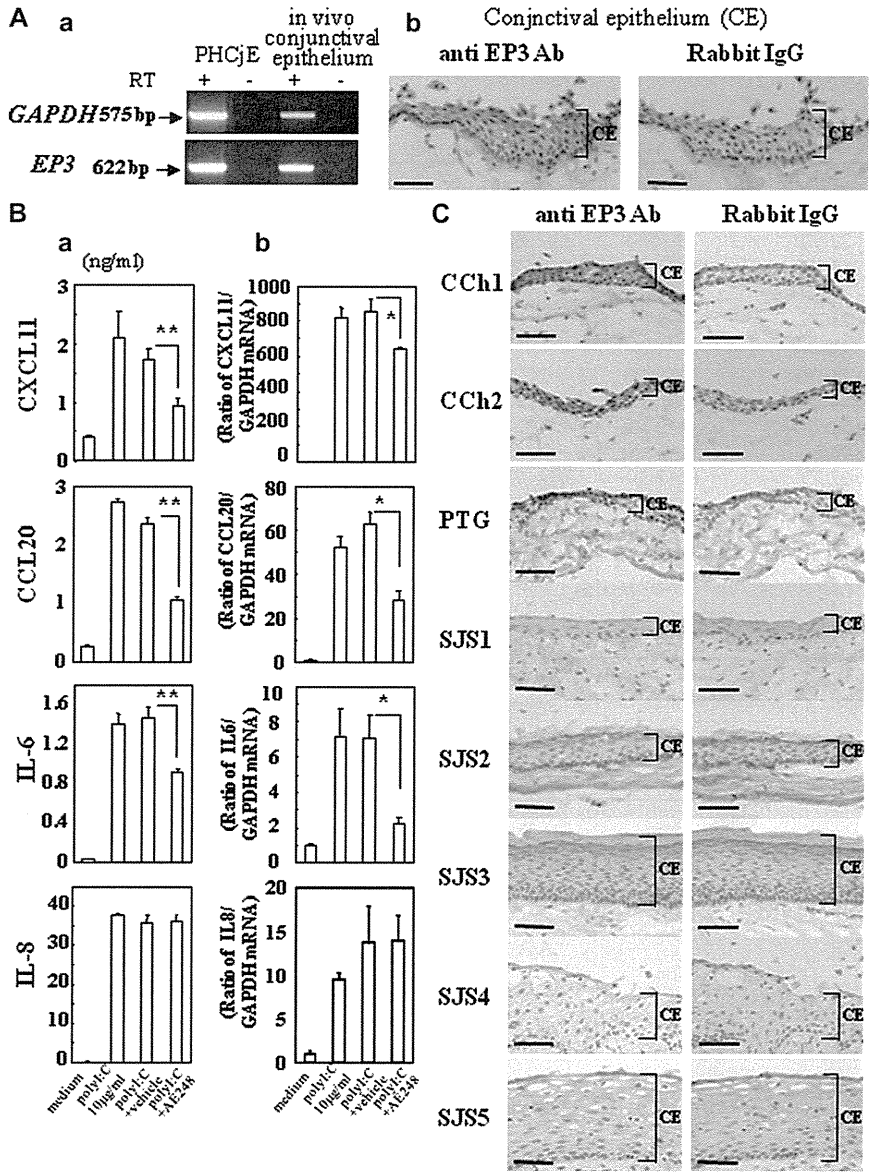

FIG 3. Expression and functional analyses of EP3 in human CE cells. **A**, *EP3* mRNA and EP3 protein expression in the human CE. *a*, RT-PCR analysis of *EP3* mRNA in normal human CE. *b*, Immunohistological analysis of EP3 in normal human conjunctival tissues. *Bars* = 50 μm. **B**, Suppression of cytokine production by an EP3 agonist. Pretreatment with ONO-AE248 significantly suppressed the protein *(a)* and mRNA *(b)* levels of CXCL11, CCL20, and IL-6 but not IL-8. Data are representative of 6 separate experiments for proteins and 2 separate experiments for mRNA. Data show the mean ± SEM from an experiment carried out in 6 wells for protein and 4 wells for mRNA per group. $*P < .05$, $**P < .01$. **C**, Reduced EP3 protein expression in the CE of patients with SJS/TEN. *CCh*, Conjunctivochalasis; *PTG*, pterygium; *SJS*, SJS/TEN. Each *bar* represents 50 μm.

control CE samples from patients with conjunctivochalasis or pterygium, we could not detect EP3 protein in the CE samples from patients with SJS/TEN (Fig 3, *C*). These results suggest that EP3, which is a receptor for PGE_2, was downregulated in the CE of patients with SJS/TEN.

DISCUSSION

In this study we performed a GWAS to identify genetic markers associated with SJS/TEN. Because of the extremely low prevalence of the disease, our GWAS was quite challenging to perform because of the sample size, which directly affects the statistical power to detect significant SNPs. As expected from the phenotype of SJS/TEN (which has been considered to be multifactorial), the low power of the study design, or both, we could not obtain genome-wide significant SNPs associated with the disease (see Fig E3 in this article's Online Repository at www.jacionline.org). However, we were able to demonstrate that as long as functional evidence could be obtained, it was worthy to perform a GWAS to list-up the candidate gene or genes or region or regions to choose and carry out follow-up functional studies. Therefore the concept of this study should shed light on future studies aimed at identifying genetic markers associated with diseases with low prevalence.