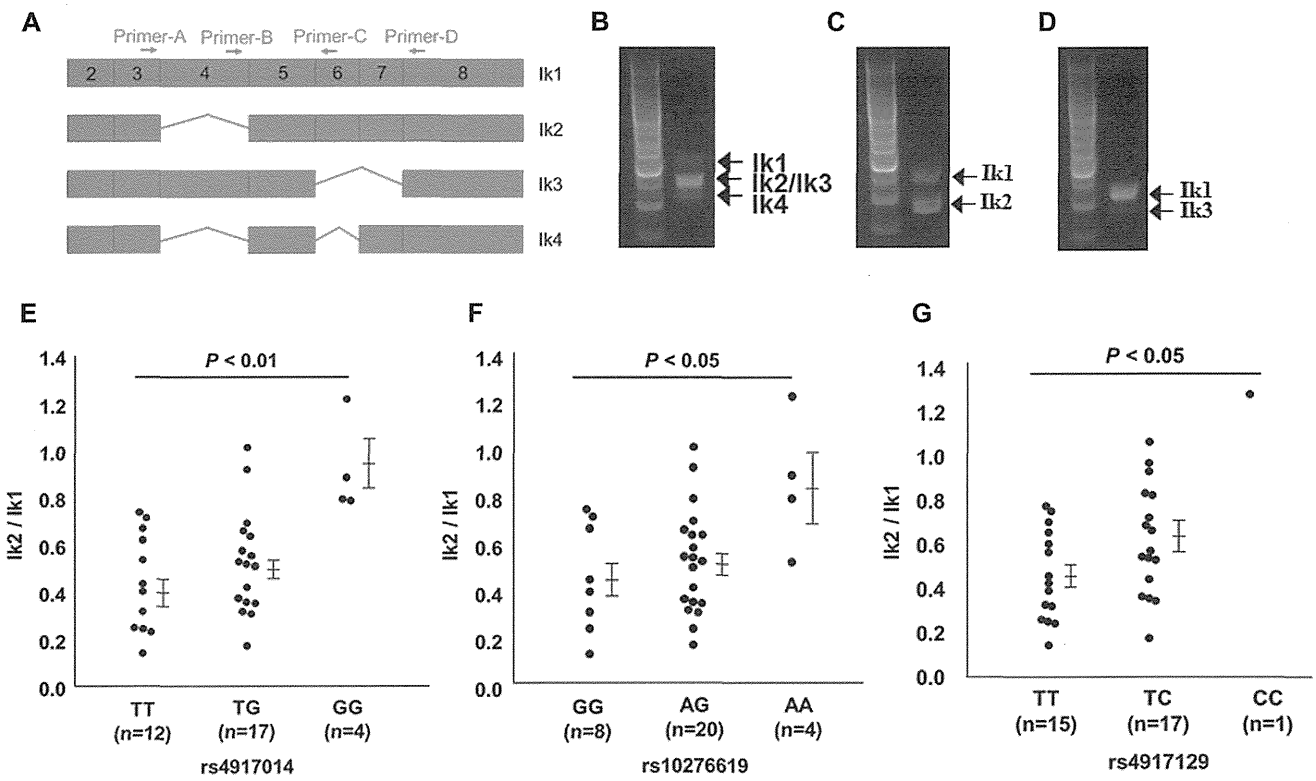

FIG 2. *IKZF1* SNPs (rs4917014, rs10276619, and rs4917129) were significantly associated with the efficiency of alternative splicing of *IKZF1* mRNA. **A,** There are 4 major splicing isoforms in *IKZF1* mRNA. Primers for semiquantitative RT-PCR are shown with *red arrows*. **B-D,** Band patterns of each amplicon of *IKZF1* alternative splicing isoforms using quantitative RT-PCR. Ik1, Ik2/Ik3 (same molecular size), and Ik4 can be detected by primer A and primer D (Fig 2, *B*). Ik1 and Ik2 can be detected by primer A and primer C (Fig 2, *C*). Ik1 and Ik3 can be detected by primer B and primer D (Fig 2, *D*). **E-G,** Ik2/Ik1 ratios are increased in whole blood cells from healthy subjects with the rs4917014-GG (Fig 2, *E*), rs10276619-AA (Fig 2, *F*), or rs4917129-CC (Fig 2, *G*). *Dots* show the Ik2/Ik1 ratio in each subject, and means ± SEMs are shown. $P <$ .01 (rs4917014) and $P <$ .05 (rs10276619 and rs4917129), Jonkheere-Terpstra test. Representative results from 3 independent experiments are shown.

might be a universal marker for susceptibility to CM-SJS/TEN with SMI.

We also found that the relative quantity of Ik2 (*IKZF1* isoform lacking exon 4–encoded amino acids) was significantly lower in subjects with the susceptible genotypes at *IKZF1* SNPs.

We previously reported that Toll-like receptor 3 *(TLR3)*,[1,23,34] IL-4 receptor *(IL4R)*,[18,19] *IL13*,[19] Fas ligand *(FASL)*,[20] and prostaglandin E receptor 3 *(PTGER3)*[14,34] SNPs showed significant associations with SJS/TEN with severe ocular surface complications. Moreover, we also reported that about 80% of our patients with CM-SJS/TEN had taken cold medicines, such as NSAIDs and multi-ingredient cold medications, for common cold symptoms within several days before disease onset.[14] Here we focused on CM-SJS/TEN with SMI (including severe ocular surface complications) and performed a GWAS followed by replication studies, concluding that *IKZF1* was significantly associated with CM-SJS/TEN with SMI. A meta-analysis with Japanese, Korean, Indian, and Brazilian subjects confirmed the significant association between the SNP rs4917014 in the *IKFZ1* locus and CM-SJS/TEN with SMI. To our knowledge, this is the first report of a genome-wide significant association between a non-*HLA* gene and CM-SJS/TEN with SMI.

SJS/TEN comprises various phenotypes, including both with SMI and without SMI, and the causative drugs also vary; for example, carbamazepine, allopurinol, and cold medicines, including NSAIDs and multi-ingredient cold medications, can independently elicit SJS/TEN. We reported that HLA-mediated genetic predispositions for SJS/TEN with SMI might differ from those for SJS/TEN without SMI.[16] The *IKZF1* SNP rs4917014 was not significantly associated with CM-SJS/TEN without SMI, such as severe ocular surface complications (cases, n = 16; control subjects, n = 877; rs4917014 [G vs T]: OR, 1.34; P = .41), and the OR of this SNP showed the opposite direction of association with CM-SJS/TEN with SMI, suggesting that the *IKZF1* SNPs are significantly associated with CM-SJS/TEN with SMI but not CM-SJS/TEN without SMI.

Each causative drug has different genetic predispositions; for example, carbamazepine-induced SJS/TEN is associated with *HLA-B*15:02*[7] or *HLA-A*31:01*,[8,9] and allopurinol-induced SJS/TEN is associated with *HLA-B*58:01*[10-12] (see Fig E6 in this article's Online Repository at www.jacionline.org). Interestingly, the *IKZF1* SNPs were not significantly associated with mild or moderate cold medicine–related adverse cutaneous reactions (not severe types; see Table E8 in this article's Online Repository at www.jacionline.org). It is possible that additional genetic factors could be identified by focusing on each distinct clinical phenotype, as in the case of the present study

on CM-SJS/TEN with SMI, including severe ocular surface complications.

In the present study we found that CM-SJS/TEN with SMI was highly significantly associated with the *IKZF1* gene. Previous studies reported that Ikaros, the protein product encoded by *IKZF1*, is a member of the DNA-binding protein family and works as a transcription factor in the thymus, spleen, peripheral blood lymphocytes, and lymph nodes. Ikaros plays an important role in the development of several lymphocytes, such as T and B cells.[35] There are dominant-negative forms of Ikaros that cannot bind to DNA.[36] Ikaros 2 (Ik2 isoform) and Ikaros 4 (Ik4 isoform) lack the DNA-binding ability and seem to be dominant-negative forms. In our present study the quantity of the Ik2 isoform is increased in disease-protective genotypes of *IKZF1* (rs4917014 G/G and rs10276619 A/A). As shown in Fig 2, the number of N-terminus zinc-finger domains of the Ik2 isoform is less than that of the Ik1 isoform. Taken together, these results indicated that the *IKZF1* Ik2 isoform might work as a dominant-negative form against the Ik1 isoform by having fewer N-terminus Zinc-finger domains in effector cells in the immune system, and the failure of immune tolerance by excess signaling in the antigen receptors is prevented by this dominant-negative isoform. Furthermore, interferon regulatory factors (IRFs) are implicated in regulating Ikaros.[36,37] IRF-5 and IRF-8 control the expression of *IKZF1* and Ikaros, thereby regulating the induction of inflammatory cytokines and type 1 interferons. Because TLRs are located upstream of IRFs, innate immunity might be associated with the regulation of Ikaros; this hypothesis is consistent with our previous findings that SJS/TEN might be associated with abnormalities of innate immunity.[1,34,38]

Although rs4917014, rs10276619, and rs4917129 are located in the 5′ region of *IKZF1* and the distances between these SNPs and *IKZF1* exon 1 are greater than 50 kb, our present results indicate that these SNPs play some role in the efficiency of *IKZF1* alternative splicing. These SNPs and the 5′ part of the *IKZF1* gene are located in the same linkage disequilibrium block. Therefore some polymorphisms that are in the same linkage disequilibrium block with rs4917014, rs10276619, and rs4917129 are probably located in a splice site or splicing regulatory motif (ie, exonic splicing enhancer, exonic splicing silencer, intronic splicing enhancer, or intronic splicing silencer) that regulates *IKZF1* alternative splicing, and these polymorphisms might alter the efficiency of alternative splicing. Further investigations and analysis are needed to elucidate the role of *IKZF1* in *the* pathogenesis of CM-SJS/TEN with SMI and to identify the causal variants related to the regulation of alternative splicing.

Interestingly, it is reported that the *IKZF1* SNP (rs4917014) has been associated with systemic lupus erythematosus in a Chinese population.[39] However, to the best of our knowledge, our patients with CM-SJS/TEN with SMI have not had systemic lupus erythematosus.

Previously and currently, we found that the *HLA-A* region showed the strongest association with susceptibility to CM-SJS/TEN with SMI[16]; *HLA-A*02:06* was strongly associated with CM-SJS/TEN with SMI, including severe ocular complications, in Japanese populations.[16] Here we use KPUM samples from the GWAS to perform an analysis examining the relationship between the 4 relevant *IKZF1* SNPs and *HLA-A*02:06*; we found that the *IKZF1* SNPs showed significant associations in both *HLA-A*02:06*–positive and *HLA-A*02:06*–negative subjects (see Tables E9 and E10 in this article's Online Repository at www.jacionline.org).

Notably, some infectious agents can, like cold medicine, trigger SJS/TEN.[40,41] We previously reported that rs3775296T/T, an SNP genotype at *TLR3*, is a risk factor for SJS/TEN with SMI, including severe ocular complications,[1] and that the interaction between *HLA-A*02:06* and rs3775296T/T manifests more than additive effects.[23] *TLR3* is a pattern recognition receptor and is related to virally activated innate immunity, which often cause common cold symptoms.

Here, we conducted a GWAS for CM-SJS/TEN with SMI in Japanese subjects and performed replication studies with Korean, Indian, or Brazilian subjects to identify host genetic factors for CM-SJS/TEN with SMI. Our findings might expand our knowledge of pathogenic pathways in SJS/TEN with SMI.

We thank all the patients and volunteers who enrolled in our study. We also thank Ms Megumi Sageshima, Ms Yuko Hirano, Ms Natsumi Baba, Ms Rieko Shirahashi, Ms Ayumi Nakayama, and Ms Hiromi Nishigaki for processing blood samples and performing genotyping and Dr Sangchul Yoon, Dr Hyo Seok Lee, Dr Kyu-yeon Hwang, and Almas Shamaila for assistance in collecting blood and DNA samples and clinical information.

Clinical implications: Ikaros might be one of the key players in the pathogenesis of CM-SJS/TEN with SMI and could be a target for the prevention or treatment of this disease.

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METHODS

Patients

This study was approved by the Institutional Review Board of KPUM, the University of Tokyo, and the National Institute of Health Sciences. Moreover, this study was also approved by the Institutional Review Boards of Seoul National University College of Medicine; Yonsei University College of Medicine; Chonnam National University Medical School and College of Medicine; the Catholic University of Korea; the L V Prasad Eye Institute in Hyderabad, India; and the Federal University of São Paulo, Brazil.

All experimental procedures were conducted in accordance with the principles of the Declaration of Helsinki. The purpose of the research and the experimental protocols was explained to all participants, and each provided prior written informed consent for their participation.

Samples from 117 patients with CM-SJS/TEN with SMI used for the GWAS and DigiTaq2 assay were collected at KPUM. Of the 117 patients with CM-SJS/TEN with SMI, 46 were male and 71 were female, and their ages ranged from 6 to 85 years (median age, 41.5 ± 17.1 [SD] years). The age at onset of SJS/TEN ranged from 1 to 70 years (median age at onset, 24.6 ± 16.2 [SD] years). For some patients, the specific drug or drugs used are not known. Healthy Japanese volunteers served as the control subjects for the GWAS (n = 691) and DigiTaq2 assay (n = 689). They were independently recruited by the University of Tokyo (n = 419; 350 female and 69 male subjects; unknown ages) and by KPUM (n = 270; 158 female and 112 male subjects; median age, 33.9 ± 10.1 [SD] years).

For the replication study, samples from 16 Japanese patients (11 female and 5 male patients) who had recently developed CM-SJS/TEN with SMI, including pseudomembrane formation and epithelial defects of the ocular surface (median age, 35.6 ± 18.1 [SD] years, which was the same as the median age at onset), were collected by participating institutes or through a nationwide blood sampling network operated by the National Institute of Health Sciences in cooperation with the Ministry of Health, Labour and Welfare; the Pharmaceutical and Medical Devices Agency; and the Federation of Pharmaceutical Manufacturers' Association of Japan. The criteria proposed by Bastuji-Garin et al were used for the diagnosis of SJS/TEN. Additional healthy Japanese volunteers recruited by the University of Tokyo (n = 188; 95 female and 93 male subjects; median age, 54.1 ± 8.0 [SD] years) served as control subjects.

For analysis of the 4 *IKZF1* SNPs, we could include 16 additional samples from Japanese patients with CM-SJS/TEN collected at KPUM, 6 from male and 10 from female patients (median age, 50.8 ± 18.3 [SD] years). The age at onset of SJS/TEN ranged from 4 to 64 years (median age at onset, 26.0 ± 17.0 [SD] years).

For the replication study, samples from Korean patients with CM-SJS/TEN with SMI were collected from the Seoul National University College of Medicine, Yonsei University, Chonnam National University, and the Catholic University of Korea. Samples were collected from 27 patients (10 male and 17 female patients) ranging in age from 4 to 66 years (median age, 34.2 ± 18.1 [SD] years), and the age at onset of SJS/TEN ranged from 3 to 63 years (median age at onset, 22.6 ± 16.2 [SD] years). Moreover, for analysis of the 4 *IKZF1* SNPs, we could include 4 additional samples from Korean patients with CM-SJS/TEN. We analyzed the 4 *IKZF1* SNPs in 31 samples from Korean patients with CM-SJS/TEN with SMI (11 male and 20 female patients; median age, 36.0 ± 19.1 [SD] years; median age at onset, 25.2 ± 17.4 [SD] years). Healthy Korean volunteers (n = 90; 35 male and 55 female subjects; median age, 31.7 ± 7.9 [SD] years) served as control subjects.

For the replication study, samples from Indian patients with CM-SJS/TEN with SMI were collected from the L V Prasad Eye Institute (n = 20; 12 male and 8 female patients; age range, 7-63 years; median age, 27.1 ± 13.4 [SD] years). The age at onset of SJS/TEN ranged from 3 to 42 years (median age at onset, 19.2 ± 12.2 [SD] years; unknown age of onset for 8 patients). Healthy Indian volunteers (n = 58; 31 male and 27 female subjects; median age, 36.3 ± 12.3 [SD] years) served as control subjects.

For the replication study, samples from Brazilian patients with CM-SJS/TEN with SMI were collected from the Federal University of São Paulo (n = 39; 15 male and 24 female patients; age range, 13-69 years; median age, 36.5 ± 15.7 [SD] years). Age at onset of SJS/TEN ranged from 3 to 69 years (median age at onset, 23.6 ± 16.9 [SD] years). Healthy Brazilian volunteers (n = 135; 55 male and 79 female subjects; median age, 41.1 ± 12.8 [SD] years) served as control subjects.

For Japanese cases and control subjects from KPUM, genomic DNA was isolated from peripheral blood by SRL (Tokyo, Japan). For Japanese cases from the National Institute of Health Sciences, genomic DNA was isolated from peripheral blood by Mitsubishi Chemical Medience Corporation (Tokyo, Japan). For samples from Korean subjects, the PAXgene Blood DNA kit (Qiagen, Hilden, Germany) was used to extract DNA from whole peripheral blood. For sampled from Indian subjects, DNA was extracted from whole peripheral blood with the phenol chloroform method.

For Japanese GWAS control samples from the University of Tokyo, a commercial kit (QIAamp Blood Kit; Qiagen, Hilden, Germany) was used to extract genomic DNA from peripheral blood samples. All 419 blood and DNA samples were deidentified. Verbal informed consent was obtained from all participants before 1990. In this study written informed consent was not obtained because blood sampling was conducted before the "Ethical guidelines for human genome and genetic sequencing research" were established in Japan. Under the condition that the DNA samples were permanently delinked from the subjects, this study was approved by the Research Ethics Committee of Graduate School of Medicine, University of Tokyo. For Japanese replication control samples, genomic DNA samples were provided by Health Science Research Resources Bank (Osaka, Japan).

Semiquantitative RT-PCR of *IKZF1* transcript isoforms

Healthy volunteers were recruited from the University Hospital at KPUM. All subjects provided informed consent for genetic testing and quantification of gene transcripts under the approval of the ethics committee of KPUM. Venous blood samples were collected from the volunteers. DNA was extracted from whole blood samples by SRL. PureLine Total RNA Blood Purification Kits (Invitrogen, Carlsbad, Calif) were used to extract total RNA from whole blood samples.

Genotyping of rs4917014, rs10276619, and rs4917129 was performed with the TaqMan genotyping method. The ratios of Ik1 (full-length *IKZF1* isoform) and each *IKZF1* splicing isoform were estimated by means of semiquantitative RT-PCR. RT-PCR was performed with the primer sets shown in Fig 2, *A*, and Table E1 and Fast-Start Taq DNA polymerase (Roche) to detect Ik2, Ik3, and Ik4 isoforms. To achieve linear amplification for the detection of Ik2 (exon 4–skipping isoform), Ik3 (exon 6 and exon 7–skipping isoform), or Ik4 (exon 4 and exon 6–skipping isoform), 28, 30, or 29 amplification cycles were found to be optimal in preliminary experiments, respectively; each cycle comprised incubations at 98°C for 5 seconds, 55°C for 10 seconds, and 72°C for 5 seconds in the GeneAmp PCR system 9700 (Perkin-Elmer Applied Biosystems). After electrophoresis of PCR amplicons through 1% agar gel, band intensities were quantified with Image J software (National Institute of Health, Bethesda, Md). These experiments were repeated 3 times with essentially identical results. The nonparametric Jonckheere-Terpstra test and Kruskal-Wallis test were used for statistical analysis.

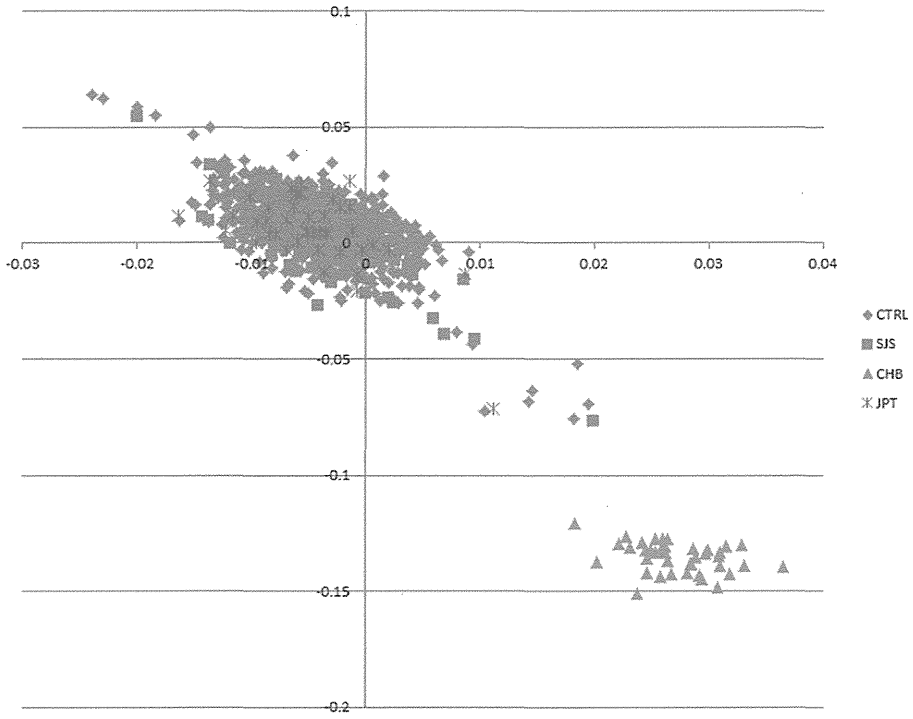

FIG E1. Principal component analysis.

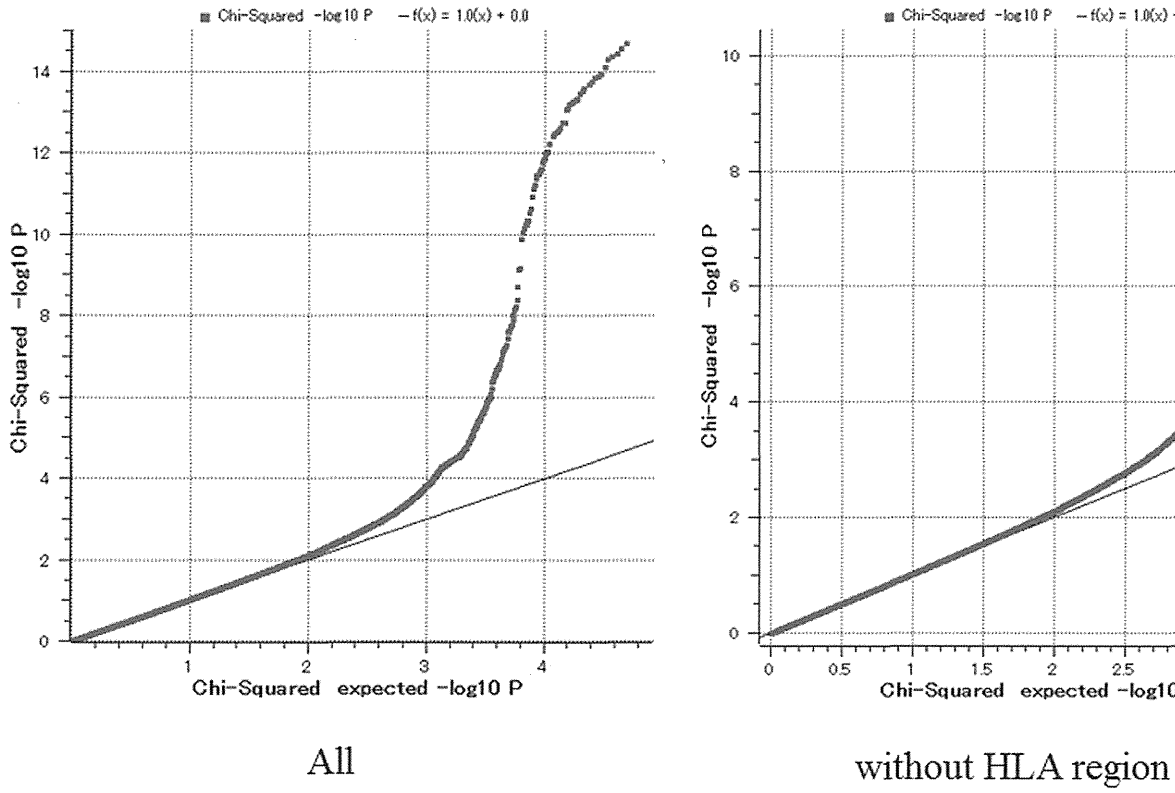

FIG E2. Quantile-quantile plot of the distribution of test statistics for comparison of genotype frequencies in cases and control subjects.

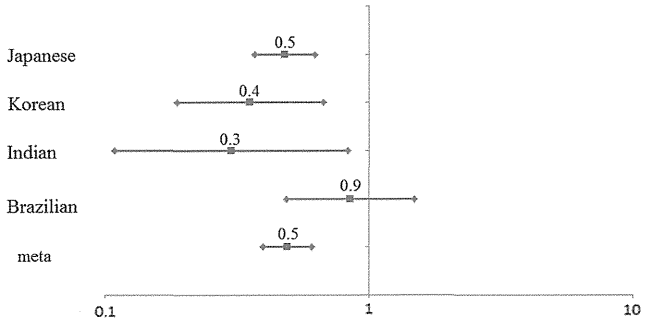

FIG E3. Forest plot presenting ORs in 4 populations and meta-analysis on rs4917014 in *IKZF1*. *Horizontal lines* represent 95% CIs.

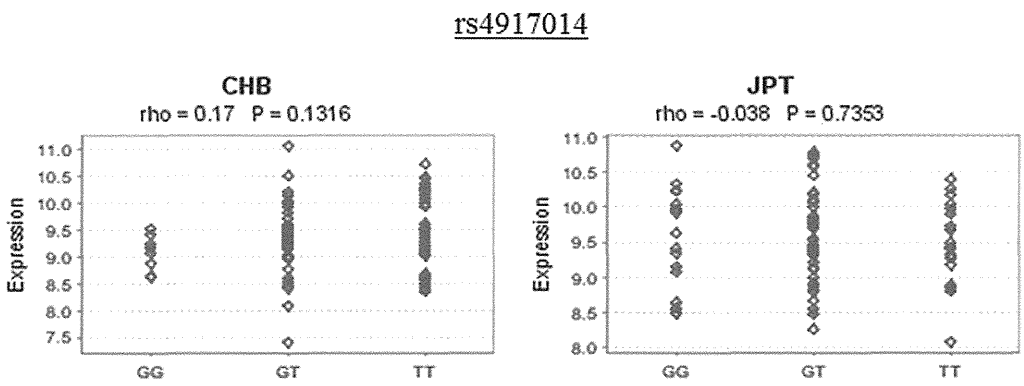

FIG E4. No significant association between rs4917014 genotype and *IKZF1* gene expression level based on GENEVAR (GENe Expression VARiation, Wellcome Trust Sanger Institute) database.

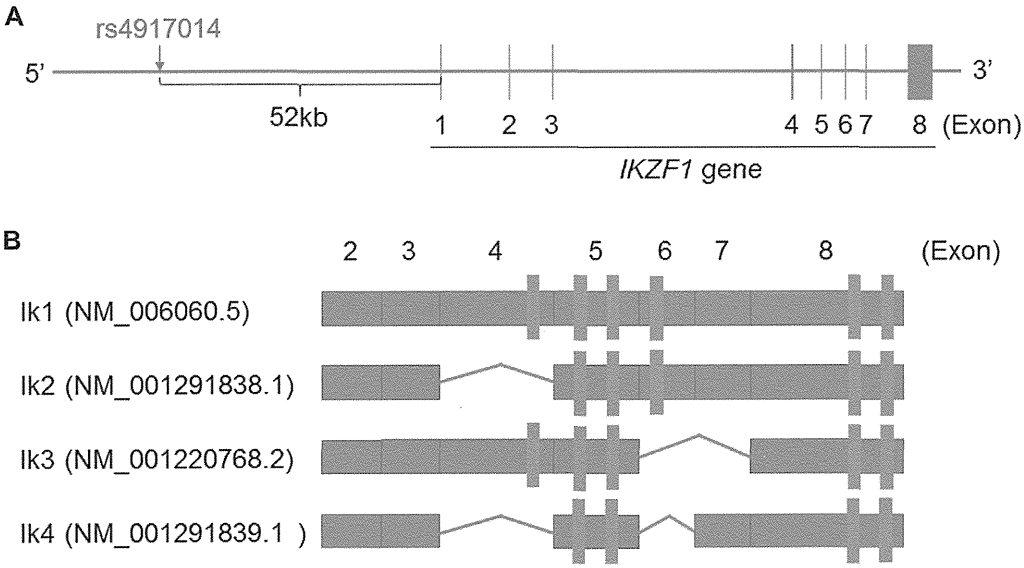

FIG E5. The location of rs4917014 and accession numbers of each *IKZF1* isoform.

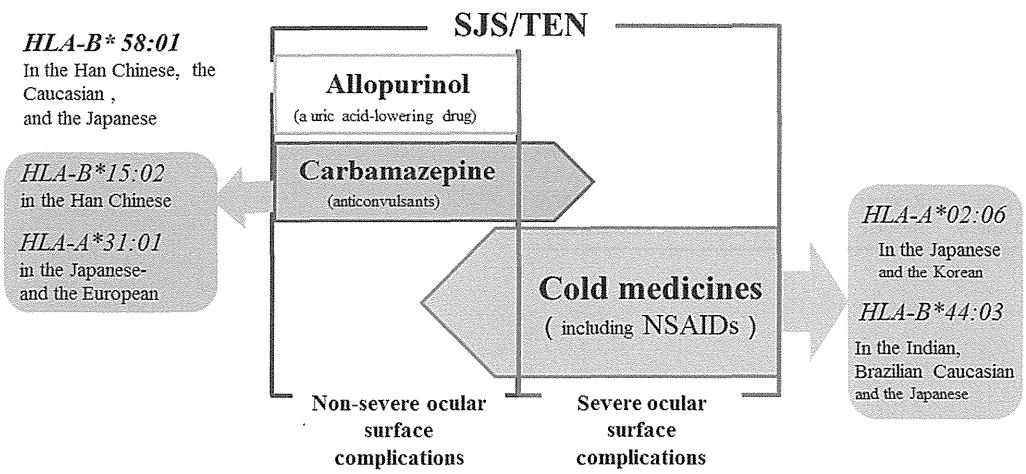

FIG E6. Particular *HLA* alleles are associated with different causative drugs.

TABLE E1. Primer sets for detecting IK1, Ik2, Ik3, and Ik4 isoforms

Name	Location	Forward or reverse	Sequence
IKZF1, primer A	Exon 2	Forward	GCTGATGAGGGTCAAGACAT
IKZF1, primer B	Exon 4	Forward	TCATTTGCATCGGGCCCAAT
IKZF2, primer C	Exon 6	Reverse	AGCTTCGGCCACAATATCCA
IKZF2, primer D	Exon 8	Reverse	TCGTTCTCCTTCTCGTAGCT

TABLE E2. Replication analysis with Japanese population 2

Patients with SJS, n = 16; control subjects, n = 188				Allele (1 vs 2)		Minor allele frequency	
Gene symbol	**rs no.**	**Minor allele (1)**	**Major allele (2)**	***P* value (χ^2 test)**	**OR (95% CI)**	**Cases**	**Control subjects**
LOC148709	rs10800873	A	C	.407	0.6 (0.2-1.9)	0.125	0.184
IGSF11	rs4687960	C	T	.194	0.4 (0.1-1.7)	0.063	0.145
FUT9	rs11153964	T	G	.029	2.2 (1.1-4.7)	0.438	0.258
FUT9	rs2294839	C	T	.013	2.5 (1.2-5.2)	0.438	0.238
IKZF1	rs897693	C	T	.236	2.1 (0.6-7.7)	0.094	0.046
IKZF1	rs4917014	G	T	.074	0.5 (0.2-1.1)	0.344	0.508
TMCC3	rs4761639	T	C	.583	1.3 (0.6-2.8)	0.281	0.238
TSHZ2	rs4809905	A	G	.752	0.9 (0.4-2.0)	0.281	0.308

TABLE E3. Meta-analysis of the 8 SNPs using samples from Japanese and Korean subjects

Patients with SJS, n = 160; control subjects, n = 967		Minor allele (1)	Major allele (2)	Allele (1 vs 2)	
Gene symbol	**rs no.**			***P* value***	**OR (95% CI)**
LOC148709	rs10800873	A	C	2.11E-03	1.6 (1.2-2.1)
IGSF11	rs4687960	C	T	5.25E-05	0.4 (0.2-0.6)
FUT9	rs11153964	T	G	2.10E-06	1.8 (1.4-2.3)
FUT9	rs2294839	C	T	3.13E-07	2.0 (1.5-2.5)
IKZF1	rs897693	C	T	5.05E-06	3.0 (1.8-5.0)
IKZF1	rs4917014	G	T	**9.49E-10**	0.5 (0.4-0.6)
TMCC3	rs4761639	T	C	1.66E-04	1.6 (1.3-2.1)
TSHZ2	rs4809905	A	G	5.52E-05	0.6 (0.4-0.7)

Values in boldface indicate statistical significance in the genome-wide association.
*Cochran-Mantel-Haenszel method.

TABLE E4. Results of analysis of the 4 *IKZF1* SNPs: Japanese samples

Patients with SJS, n = 149; control subjects, n = 877			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	Minor allele (1)	Major allele (2)	*P* value (χ^2 test)	Corrected *P* value	OR (95% CI)	11	12	22	11	12	22
rs897693	C	T	2.16E-06	8.62E-06	3.2 (1.9-5.4)	0	24	125	4	38	828
rs4917014	G	T	2.99E-08	1.20E-07	0.5 (0.4-0.6)	16	62	71	204	449	224
rs4917129	C	T	4.12E-06	1.65E-05	0.5 (0.4-0.7)	15	61	73	172	442	263
rs10276619	G	A	1.28E-06	5.14E-06	1.8 (1.4-2.4)	53	69	27	155	454	267

TABLE E5. Results of analysis of the 4 *IKZF1* SNPs: Korean samples

Patients with SJS, n = 31; control subjects, n = 90			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	Allele (1)	Allele (2)	*P* value (χ^2 test)	Corrected *P* value	OR (95% CI)	11	12	22	11	12	22
rs897693	C	T	.406	—	1.8 (0.4-7.9)	0	3	27	0	5	85
rs4917014	G	T	**1.20E-03**	4.80E-03	0.4 (0.2-0.7)	2	12	17	20	49	21
rs4917129	C	T	**4.32E-03**	1.73E-02	0.4 (0.2-0.8)	3	10	21	19	39	31
rs10276619	G	A	**1.20E-03**	4.79E-03	2.7 (1.5-4.9)	13	16	2	17	45	28

Values in boldface indicate statistical significance.

TABLE E6. Results of analysis of the 4 *IKZF1* SNPs: Indian samples

Patients with SJS, n = 20; control subjects, n = 56			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	Allele (1)	Allele (2)	*P* value (χ^2 test)	Corrected *P* value	OR (95% CI)	11	12	22	11	12	22
rs897693	C	T	.891	—	1.1 (0.5-2.2)	4	10	6	9	31	16
rs4917014	G	T	**.016**	.065	0.3 (0.1-0.8)	0	5	15	7	22	27
rs4917129	C	T	.057	—	0.5 (0.2-1.0)	3	6	11	14	25	17
rs10276619	G	A	0.509	—	1.4 (0.5-3.5)	0	8	12	2	13	40

Value in boldface indicates statistical significance.

TABLE E7. Results of analysis of the 4 *IKZF1* SNPs: Brazilian samples

Patients with SJS, n = 39; control subjects, n = 135			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	**Allele (1)**	**Allele (2)**	***P* value (χ^2 test)**	**Corrected *P* value**	**OR (95% CI)**	**11**	**12**	**22**	**11**	**12**	**22**
rs897693	C	T	.568	—	1.2 (0.6-2.4)	0	13	26	3	32	100
rs4917014	G	T	.581	—	0.9 (0.5-1.5)	2	18	19	12	61	62
rs4917129	C	T	.112	—	0.7 (0.4-1.1)	8	20	11	44	63	27
rs10276619	G	A	.118	—	1.5 (0.9-2.5)	9	19	11	21	58	54

TABLE E8. Replication analysis for Japanese subjects with cold medicine–induced cutaneous adverse reaction (not severe types)

rs no.	Minor allele (1)	Major allele (2)	Cases, no.		Control subjects, no.		Basic allele (1 vs 2)	
			1	2	1	2	*P* value (χ^2 test)	OR (95% CI)
rs897693	C	T	5	137	50	1714	.638	1.3 (0.5-3.2)
rs4917014	G	T	71	71	770	922	.603	1.2 (0.9-1.7)
rs4917129	C	T	69	73	776	988	.288	1.2 (0.9-1.7)
rs10276619	G	A	59	83	775	989	.582	1.1 (0.8-1.5)

TABLE E9. Relation between *HLA-A*02:06* and the 4 IKZF1 SNPs in Japanese population 1: Analysis of *HLA-A*02:06*–positive samples

Patients with SJS, n = 58; control subjects, n = 94			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	Minor allele (1)	Major allele (2)	*P* value (χ^2 test)	Corrected *P* value	OR (95% CI)	11	12	22	11	12	22
rs897693	C	T	.134	—	2.2 (0.8-6.6)	0	8	50	1	4	89
rs4917014	G	T	**3.53.E-04**	1.41E-03	0.4 (0.3-0.7)	5	25	28	21	54	19
rs4917129	C	T	**5.83.E-04**	2.33E-03	0.4 (0.3-0.7)	6	21	31	19	53	22
rs10276619	G	A	**7.33.E-04**	2.93E-03	2.2 (1.4-3.6)	21	28	9	14	48	32

Values in boldface indicate statistical significance.

TABLE E10. Relation between *HLA-A*02:06* and the 4 IKZF1 SNPs in Japanese population 1: Analysis of *HLA-A*02:06*–negative samples

Patients with SJS, n = 59; control subjects, n = 595			Basic allele (1 vs 2)			Cases, no.			Control subjects, no.		
rs no.	Allele (1)	Allele (2)	*P* value (χ^2 test)	Corrected *P* value	OR (95% CI)	11	12	22	11	12	22
rs897693	C	T	**1.37E-07**	5.48E-07	5.7 (2.8-11.8)	0	12	47	1	21	570
rs4917014	G	T	**2.04.E-03**	8.16E-03	0.5 (0.4-0.8)	8	23	28	133	304	158
rs4917129	C	T	0.0269	0.108	0.6 (0.4-1.0)	7	25	27	113	293	189
rs10276619	G	A	0.0127	0.0507	1.6 (1.1-2.4)	21	25	13	112	309	174

Values in boldface indicate statistical significance.