in use situations including flexing, massage (Leite-Silva et al., 2016a), occlusion (Leite-Silva et al., 2016b), repeated hourly and daily application (Mohammed et al., 2019), and now bathing. Health promotion organizations, healthcare professionals, teachers, and parents can confidently recommend the use of effective nanoparticle-based sunscreens to protect children and adults from sunburn, skin cancer, and photo-aging.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Association of HLA-A*11:01 with Sulfonamide-Related Severe Cutaneous Adverse Reactions in Japanese Patients

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TO THE EDITOR

Sulfonamides are pharmaceuticals with an SO_2-NH_2 group, used mainly for treating infectious and inflammatory diseases. Their main active ingredient is sulfanilamide (SN), a metabolite that can inhibit folic acid synthesis in bacteria. In Japan, common sulfonamides include sulfamethoxazole (SMX) and salazosulfapyridine (SASP). Sulfonamides can cause severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug-induced hypersensitivity syndrome (Schnyder and Pichler, 2013). Dapsone (4,4′-diaminodiphenylsulfone) is a well-known sulfone drug that also causes SCARs, and *HLA-B*13:01* is associated with hypersensitivity to dapsone (Zhang et al., 2013). However, dapsone is not a sulfonamide because it does not release SN. Therefore, it is possible that other HLA types may be

Abbreviations: NAT2, N-acetyltransferase 2; SA, slow acetylator; SASP, salazosulfapyridine; SCAR, severe cutaneous adverse reaction; SMX, sulfamethoxazole; SN, sulfanilamide

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Table 1. Association Between the *HLA-A*11:01* Allele and Sulfonamide-Related SJS or TEN and DIHS

Variables	Control (N = 2,878)	SJS/TEN (N = 8)	DIHS (N = 7)	All SCARs (N = 15)
*HLA-A*11:01*-positive	486	6	4	10
*HLA-A*11:01*-negative	2,392	2	3	5
OR		14.77	6.56	9.84
95% confidence interval		2.97–73.4	1.46–29.4	3.35–28.9
Fisher's exact *P*		4.91×10^{-4}	0.0187	2.67×10^{-5}
P corrected (Pc)[1]		0.0034	0.1309	2.14×10^{-4}

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
[1]*P*c values were calculated by multiplying the "number of detected *HLA-A* alleles" (i.e., seven for SJS or TEN, seven for DIHS, and eight for All SCARs) and the corresponding Fisher's exact *P* values.

associated with the onset of SCARs caused by SMX and SASP.

Sulfonamides are known to be metabolized by N-acetyltransferase 2 (NAT2). The *NAT2* gene is highly polymorphic, and its enzymatic activity is associated with seven SNPs for **5*, **6*, **7*, **11*, and **12* (McDonagh et al., 2014). The NAT2 activity phenotype is often categorized by its genotype as a rapid acetylator, intermediate acetylator, or slow acetylator (SA). The association of SA with sulfonamide hypersensitivity is still controversial (Alfirevic et al., 2003; Rieder et al., 1991).

In this study, we included 15 patients who had sulfonamide-related SCARs and 2,878 healthy volunteers as controls under the approval of all institutional ethics committees with written informed consent from each patient and subject. Eight of the patients experienced Stevens-Johnson syndrome or toxic epidermal necrolysis, and seven experienced drug-induced hypersensitivity syndrome (Supplementary Table S1). In the SCAR patients, two were possible, and the remainder of patients were probable when sulfonamide causality was assessed by the Naranjo score (Naranjo et al., 1981). Coadministered drugs for the SCAR patients are listed in Supplementary Table S2. We first searched the associated HLA-*A*, *-B*, *-C*, and *-DRB1* types for the eight patients who had Stevens-Johnson syndrome or toxic epidermal necrolysis (Supplementary Table S3). Six out of eight had *HLA-A*11:01*, which showed a statistically significant association even after correction for multiple comparisons (*P* corrected [*P*c] = 0.0034; OR, 14.77) (Table 1). This association was replicated in the seven patients with drug-induced hypersensitivity syndrome ($P = 0.0187$); four of these patients were positive for *HLA-A*11:01*. Overall, 10 of 15 patients had the *HLA-A*11:01* allele and the association was significant ($P = 2.67 \times 10^{-5}$; OR, 9.84).

Next, we examined the *NAT2* alleles and acetylator status of these 15 patients (Supplementary Table S4). A statistical comparison between rapid acetylator and SA allele frequencies and those of the healthy Japanese population showed statistical differences for drug-induced hypersensitivity syndrome and all SCAR cases (Supplementary Table S5). However, this significance disappeared after correction for multiple comparisons. The frequency of the SA phenotype based on the *NAT2* diplotype was not statistically different between SCAR patients and controls in recessive mode analysis. These results suggest that the influence of *NAT2* SA alleles and phenotypes had only marginal effects on the onset of SCARs caused by sulfonamide.

Because off-target binding of the suspected drug to a specific HLA-type molecule has been suggested as a mechanism of SCAR onset (Ostrov et al., 2012; Pichler, 2003), we performed an in silico docking simulation analysis (Goto et al., 2008) to examine possible binding of sulfonamides with the peptide-binding groove of the HLA-A*11:01 protein. Predicted binding models are shown in Figure 1. The lowest ΔG_{bind} values (kcal/mol) of the complexes between HLA-A*11:01 and SN, SMX, and SASP were −4.31, −5.60, and −6.67, respectively, and the corresponding half maximal inhibitory concentration values (μM) were estimated to be 690, 78, and 13, respectively. Arg114 and Gln156 of HLA-A*11:01 were predicted to be involved in the interactions with the three drugs (SN, SMX, and SASP) as shown in Supplementary Figure S1.

A Chinese group has reported an association between *HLA-B*13:01* and SASP-induced drug rash with eosinophilia and systemic symptoms (Yang et al., 2014). A Thai group has reported an association between the *HLA-B*15:02–C*08:01* haplotype and the onset of SCARs because of SMX (Kongpan et al., 2015). However, in the former and latter reports, four of six patients with drug rash with eosinophilia and systemic symptoms and 22 of 43 patients with SCARs were positive for the *HLA-A*11:01* allele, respectively. In both studies, because of the very high *HLA-A*11:01* allele frequencies in the control groups based on the high frequencies in their general populations, the authors may have concluded that there was no significant association with *HLA-A*11:01*. This finding could be explained by the extremely low positive predictive values of *HLA* alleles associated with idiosyncratic side effects that are generally observed (White et al., 2015). Therefore, the ratio of individuals with at-risk *HLA* alleles who do not develop side effects can be high. High-frequency *HLA* alleles in the control group did not eliminate the possibility of an association between the particular *HLA* allele and the onset of Stevens-Johnson syndrome or toxic epidermal necrolysis. The frequency of the *HLA-A*11:01* allele is lower in the Japanese population (8.2%–11.1%) than in the Chinese (15.9%–61.3%) and Thai (29.9%) populations (http://allelefrequencies.net/) (Gonzalez-Galarza et al., 2018); this facilitated the discovery of the *HLA-A*11:01* allele as a risk factor in the Japanese population. In this study, one patient (ST01) was positive for the *HLA-B*13:01* allele (Supplementary Table S3). Because this patient was negative for *HLA-A*11:01*, *HLA-*

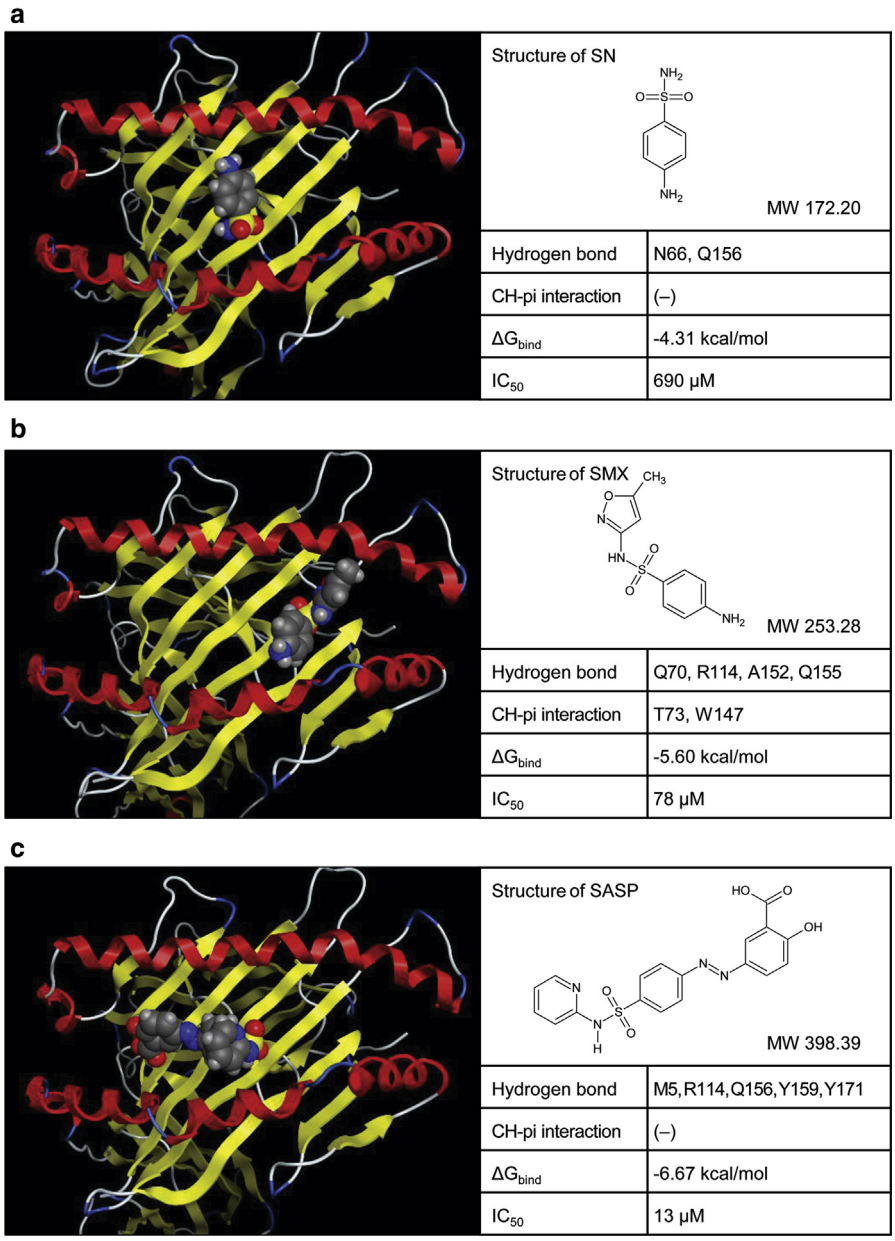

Figure 1. Interaction models of the *HLA-A*11:01* molecule and sulfonamides. (**a**) SN, (**b**) SMX, and (**c**) SASP. The *HLA-A*11:01* molecule (PDB ID 5WJL) and sulfonamides are depicted in cartoon and space-filling modes, respectively. The estimated binding free energies (ΔG_{bind}) and IC_{50} values are given. IC_{50}, half maximal inhibitory concentration; MW, molecular weight; SASP, salazosulfapyridine; SMX, sulfamethoxazole; SN, sulfanilamide.

*B*13:01* may be another sulfonamide risk factor independent of *HLA-A*11:01*.

According to the product labels used in Japan, blood concentrations of orally administered SMX (800 mg) and SASP (500 mg) at maximum serum concentration are 229 μM and 16 μM, respectively. The relationship between these blood concentrations and the simulated half maximal inhibitory concentration values (Figure 1) suggests that the parent drugs, rather than their active metabolite SN, may cause the onset of SCARs through their binding to HLA-A*11:01. Furthermore, the lower half maximal inhibitory concentration values, in comparison with the maximum serum concentration values, might be a plausible reason for the minimal influence of the *NAT2* SA phenotype.

This study was limited by its small sample size of SCAR cases and the unavailability of sulfonamide-tolerant and disease-matched controls. Therefore, additional experiments are required to confirm the association of the *HLA-A*11:01* allele with sulfonamide-related SCARs and to clarify the mechanisms underlying the pathogenesis. In addition, non-associated *HLA* alleles were not included for comparison in the docking simulation. Nevertheless, to our knowledge previously unreported, our findings suggest *HLA-A*11:01* as a risk factor for sulfonamide-related SCARs in Japanese patients.

Data availability statement

Datasets related to this letter were all presented in Tables and Figures, but raw genotyping data of *NAT2* are available on request to the corresponding author.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Conceptualization: RN, TO, TM, YS, EM; Formal analysis: RN, TO, TM, YS; Funding Acquisition: TM, YS, EM; Investigation: RN, TO, NH, AS, TY, YMa; Project Administration: TM, YS, EM; Resources: RN, YMi, TS, HW, HS, KO, HA, NK, ET, KM, HN, YY, MA, YS, EM; Writing — Original Draft Preparation: RN, YS; Writing — Review and Editing: RN, TO, NH, AS, TY, YMa, YMi, TS, HW, HS, KO, HA, NK, ET, KM, HN, YY, MA, TM, YS, EM

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2019.12.025.

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Palmoplantar Keratoderma with Leukokeratosis Anogenitalis Caused by KDSR Mutations

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TO THE EDITOR

Hereditary keratodermas and ichthyoses comprise a large collection of genodermatoses for which underlying mutations in more than 100 genes have been identified (Oji et al., 2010). The implicated genes are involved in a multitude of biological pathways. Ceramides are important for cutaneous barrier function (Borodzicz et al., 2016) and cutaneous proliferation and differentiation (Uchida, 2014). In most organisms, they are synthesized by three different biochemical pathways, named de novo, sphingomyelinase, and salvage pathways (Hannun and Obeid, 2008; Kihara, 2016; Kitatani et al., 2008). The de novo pathway (Linn et al., 2001) critically depends on 3-ketodihydrosphingosine reductase (KDSR) catalyzing the reduction of 3-ketodihydrosphingosine to dihydrosphingosine, which serves as a substrate for ceramide synthases 1–6. Recessive mutations in *CERS3* cause autosomal recessive congenital ichthyosis (Eckl et al., 2013; Radner et al., 2013). Mutations in the *ELOVL4* gene, required for the synthesis of ultra-long ceramides, are the underlying cause of a recessive disorder characterized by ichthyosis, intellectual disability, and spastic quadriplegia (Aldahmesh et al., 2011).

With great interest, we read the recent reports on mutations in the *KDSR* gene causing either autosomal recessive progressive symmetric erythrokeratoderma (Boyden et al., 2017) or a spectrum of keratinization disorders with associated thrombocytopenia characterized by palmoplantar and anogenital hyperkeratosis or a more

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SUPPLEMENTARY MATERIALS AND METHODS

Patients with Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)

Eight unrelated Japanese patients who were prescribed sulfonamides (sulfamethoxazole [SMX] or salazosulfapyridine [SASP]) for a maximum of 12 weeks before the onset of SJS or TEN were included in this study, which used a constructed system as previously described (Kaniwa et al., 2013). Patients with SJS or TEN were enrolled through a nationwide case-collecting network system in Japan that is operated by the National Institute of Health Sciences in cooperation with the Ministry of Health, Labour and Welfare; Pharmaceutical and Medical Devices Agency; and the Federation of Pharmaceutical Manufacturers' Association of Japan. SJS and TEN were defined as mucocutaneous disorders characterized by extensive erythema, blisters, epidermal detachment, erosions, enanthema, and high fever (Bastuji-Garin et al., 1993). According to the Japanese diagnostic criteria, SJS is defined as $\leq$10% skin detachment of the body surface area, and TEN is defined as >10% skin detachment of the body surface area. Information was collected using a standardized case report form that included medical records, concomitantly administrated drugs, disease progress, the involvement of systemic complications, and SJS or TEN treatment. The institutional review boards of the National Institute of Health Sciences and participating hospitals and institutes approved this study. Written informed consent was obtained from each patient. Drug causality was assessed by Naranjo and ALDEN scores (Naranjo et al., 1981; Sassolas et al., 2010).

Patients with drug-induced hypersensitivity syndrome

Seven unrelated Japanese patients with drug-induced hypersensitivity syndrome who were administered SMX or SASP at institutes belonging to the Japanese Research Committee on Severe Cutaneous Adverse Reaction (Tashiro et al., 2019) between 2004 and 2012 were enrolled in this study according to the following criteria established by the Japanese consensus group (Shiohara et al., 2007): high fever; widespread eruption; lymphadenopathy; leukocytosis with atypical lymphocytosis and/or eosinophilia; liver dysfunction; and HHV-6 reactivation. Each ethics committee of RIKEN and the participating hospitals approved this study. Written informed consent was obtained from all patients. Drug causality was assessed by the Naranjo score (Naranjo et al., 1981).

Control Subjects

Data regarding HLA-*A*, -*B*, -*C*, and -*DRB1*, as well as N-acetyltransferase 2 (NAT2) SNPs of the healthy Japanese volunteer subjects (N = 2,878), were used as the control (Kamitsuji et al., 2015). Samples were collected by the Japan PGx Data Science Consortium. Written informed consent, samples, and data were transferred to the National Institute of Health Sciences with the approval of the ethics committees of both organizations because of the dissolution of the consortium.

HLA Typing

To determine the *HLA* type, we performed PCR assays, followed by hybridization with sequence-specific oligonucleotide probes using commercial bead-based typing kits (Wakunaga, Hiroshima, Japan) according to the manufacturer's instructions. Results were read on the Luminex 100 system (Luminex Corporation, Austin, TX).

NAT2 Polymorphism Typing and Haplotype Estimation

For patients with SJS or TEN, whole-genome genotyping was conducted using Illumina Human Omni 2.5 BeadChip (Illumina, San Diego, CA) to identify major alleles (including sub-alleles) of the following seven SNPs in *NAT2*: rs1801279 (c.191G>A, p.R64Q); rs1041983 (c.282C>T, p.Y94Y); rs1801280 (c.341T>C, p.I114T); rs1799929 (c.481C>T, p.L161L); rs1799930 (c.590G>A, p.R197Q); rs1208 (c.803A>G, p.K268R); and rs1799931 (c.857G>A, p.G286E). For patients with drug-induced hypersensitivity syndrome, these seven SNPs were genotyped by target resequencing of the *NAT2* gene using the MiSeq system (Illumina) as previously described (Yoshihama et al., 2018). Haplotypes of the SNPs were estimated using Beagle 3.2 software (Browning et al., 2007). Genotypes of eight patients with SJS or TEN, seven patients with drug-induced hypersensitivity syndrome, and 2,857 healthy Japanese volunteers were incorporated into the Beagle software and phased.

Docking Simulations

A crystal structure of HLA-A*11:01 (PDB ID: 5WJL) deposited at the Protein Data Bank (Bernstein et al., 1977) was used in the docking simulations. The binding modes and affinities of sulfanilamide, SMX, and SASP to the peptide-binding groove of HLA-A*11:01 were obtained by docking simulations using ASEDock (Goto et al., 2008). The binding affinity was judged by the scoring function of generalized Born volume integral/weighted surface area (dG), which is considered to express protein-ligand binding free energy (ΔG_{bind}) (Corbeil et al., 2012). Half maximal inhibitory concentration values were calculated using the following formula:

$$\Delta G_{bind} \approx RT\ln IC_{50} \quad (1)$$

In the equation (1), R is the ideal gas constant, and T is the temperature in K (298 °K is used here). In other words, binding free energies (ΔG_{bind}) of SASP, SMX or sulfanilamide to HLA-A*11:01 molecule was used for calculation of half maximal inhibitory concentration (IC_{50}) in which inhibitor (and substrate) was HLA-A*11:01 molecule. We used half maximal inhibitory concentration value as the marker of affinity of SASP, SMX and sulfanilamide to HLA-A*11:01 molecule. The Molecular Operating Environment software system (version 2014.09, Chemical Computing Group, Quebec, Canada) was used during this study.

Statistical Analysis

We compared the carrier frequency of individual *HLA* alleles of cases and controls using Fisher's exact test (GraphPad Software; Graphpad PRISM, San Diego, CA). Similarly, the allele frequency of rapid acetylators and slow acetylators of the *NAT2* haplotype and diplotype frequencies in the recessive mode (rapid acetylators + intermediate acetylators vs. slow acetylators) of cases and controls were compared. $P < 0.05$ was considered statistically significant.

Bonferroni correction was used for multiple comparisons.

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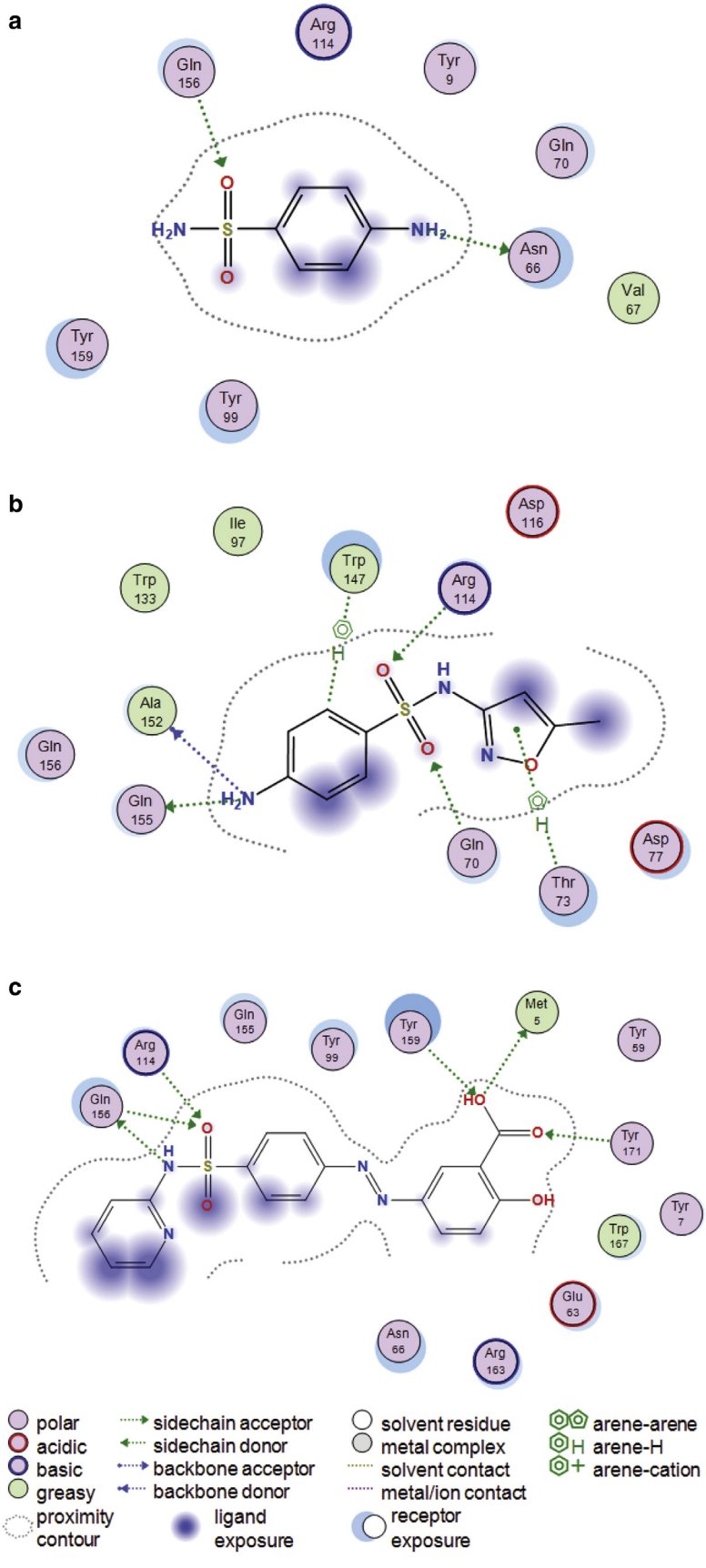

Supplementary Figure S1. Schematic of amino acid residues of the HLA-A*11:01 molecule involved in the interactions with sulfonamides. (**a**) SN, (**b**) SMX, and (**c**) SASP. SASP, salazosulfapyridine; SMX, sulfamethoxazole; SN, sulfanilamide.

Suppplementary Table S1. Demographic Characteristics of Patients with Sulfonamide-Related SJS/TEN and DIHS Included in This Study

Patient no.	Type	Sex	Age (y)	Causative drug	Dose[1] (mg/day)	Reason for administration	Days to onset	Naranjo score	ALDEN score
ST01	SJS	M	59	SMX-TMP	800	Prevention of surgical site infection	37	4	5
ST02	TEN	M	76	SMX-TMP	1,600	Pneumonia	14	6	6
ST03	SJS	M	76	SMX-TMP	2,000	Malignant rheumatoid arthritis	78	4	2
ST04	SJS	F	68	SMX-TMP	800	Malignant lymphoma	14	5	6
ST05	SJS	F	32	SMX-TMP	400	IgA nephropathy	69	7	2
ST06	SJS	F	57	SASP	1,000	Rheumatoid arthritis	16	7	6
ST07	SJS	F	66	SASP	1,000	Rheumatoid arthritis	12	7	6
ST08	SJS	F	74	SASP	500	Rheumatoid arthritis	18	6	6
D01	DIHS	F	53	SASP	1,000	Rheumatoid arthritis	14	7	
D02	DIHS	F	59	SASP	1,000	Rheumatoid arthritis, schizophrenia	27	6	
D03	DIHS	M	70	SASP	NA	Chronic rheumatoid arthritis	17	8	
D04	DIHS	F	64	SASP	1,000	Rheumatoid arthritis, bladder cancer	29	8	
D05	DIHS	F	61	SASP	3,000	Non-specific colitis	32	8	
D06	DIHS	F	64	SASP	NA	Ischemic colitis	25	8	
D07	DIHS	M	48	SMX-TMP	1,600[2]	Prevention of surgical site infection	48	8	

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; F, female; M, male; NA, not available; SASP, salazosulfapyridine; SJS, Stevens-Johnson syndrome; SMX, sulfamethoxazole; TEN, toxic epidermal necrolysis; TMP, trimethoprim.
[1]Final dose as a sulfonamide.
[2]Twice per week.

Supplementary Table S2. Concomitant Drugs for Patients with Sulfonamide-Related SJS or TEN and DIHS Included in This Study

Patient no.	Concomitant drugs
ST01	Rifampicin
ST02	Fluconazole
ST03	Omeprazole, lansoprazole, sodium alginate
ST04	Acyclovir
ST05	Famotidine, calcitriol, imidapril hydrochloride, prednisolone
ST06	Celecoxib, rebamipide
ST07	None
ST08	Loxoprofen sodium hydrate
D01	Bucillamine, celecoxib
D02	Clopidogrel sulfate, irbesartan, trichlormethiazide, atenolol, Olmesartan medoxomil, nifedipine, risperidone, biperiden hydrochloride, sennoside A·B, chlorpromazine phenolphthalinate, nitrazepam
D03	Prednisolone, teprenone
D04	Loxoprofen sodium hydrate, BCG
D05	Lactomin amylolytic bacillus, potassium chloride, famotidine
D06	None
D07	Temozolomide, tropisetron hydrochloride, rabeprazole sodium, atorvastatin calcium hydrate

Abbreviations: BCG, Bacillus Calmette-Guérin; DIHS, drug-induced hypersensitivity syndrome; TEN, toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome.

Supplementary Table S3. *HLA* Types of Patients with Sulfonamide-Related SJS or TEN and DIHS in Japan

Patient no.	Type	*HLA-A*		*HLA-B*		*HLA-C*		*HLA-DRB1*	
ST01	SJS	*A*02:01*	*A*31:01*	*B*13:01*	*B*15:01*	*C*03:03*	*C*03:04*	*DRB1*09:01*	*DRB1*12:02*
ST02	TEN	*A*11:01*	*A*33:03*	*B*15:01*	*B*44:03*	*C*04:01*	*C*14:03*	*DRB1*04:06*	*DRB1*13:02*
ST03	SJS	*A*11:01*	*A*24:02*	*B*39:01*	*B*59:01*	*C*01:02*	*C*07:02*	*DRB1*04:05*	*DRB1*15:02*
ST04	SJS	*A*11:01*	*A*26:01*	*B*15:01*	*B*40:06*	*C*04:01*	*C*08:01*	*DRB1*04:06*	*DRB1*09:01*
ST05	SJS	*A*02:06*	*A*11:01*	*B*15:01*	*B*40:02*	*C*03:04*	*C*04:01*	*DRB1*04:05*	*DRB1*04:06*
ST06	SJS	*A*02:01*	*A*11:01*	*B*13:02*	*B*51:01*	*C*06:02*	*C*15:02*	*DRB1*07:01*	*DRB1*15:01*
ST07	SJS	*A*02:06*	*A*11:01*	*B*35:01*	*B*40:01*	*C*03:03*	*C*03:04*	*DRB1*04:05*	*DRB1*11:01*
ST08	SJS	*A*24:02*	*A*31:01*	*B*15:01*	*B*52:01*	*C*03:03*	*C*12:02*	*DRB1*15:01*	*DRB1*15:02*
D01	DIHS	*A*11:01*	*A*31:01*	*B*39:01*	*B*40:01*	*C*03:04*	*C*07:02*	*DRB1*04:05*	*DRB1*08:03*
D02	DIHS	*A*11:01*	*A*11:01*	*B*55:02*	*B*56:03*	*C*01:02*	*C*01:02*	*DRB1*04:05*	*DRB1*12:01*
D03	DIHS	*A*26:01*	*A*26:02*	*B*40:02*	*B*40:06*	*C*03:04*	*C*03:04*	*DRB1*04:10*	*DRB1*09:01*
D04	DIHS	*A*11:01*	*A*24:02*	*B*39:01*	*B*67:01*	*C*07:02*	*C*07:02*	*DRB1*14:06*	*DRB1*16:02*
D05	DIHS	*A*02:06*	*A*33:03*	*B*39:01*	*B*44:03*	*C*07:02*	*C*14:03*	*DRB1*08:02*	*DRB1*13:02*
D06	DIHS	*A*11:01*	*A*26:01*	*B*39:01*	*B*51:01*	*C*07:02*	*C*15:02*	*DRB1*04:01*	*DRB1*15:01*
D07	DIHS	*A*24:02*	*A*24:02*	*B*07:02*	*B*07:02*	*C*07:02*	*C*07:02*	*DRB1*01:01*	*DRB1*01:01*

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Supplementary Table S4. Genotypes and Status of *NAT2* of Patients with Sulfonamide-Related SJS or TEN and DIHS in Japan

Patient no.	Type	rs1801279 (G191A)	rs1041983 (C282T)	rs1801280 (T341C)	rs1799929 (C481T)	rs1799930 (G590A)	rs1208 (A803G)	rs1799931 (G857A)	NAT2 genotype[1,2]	NAT2 status[3]
ST01	SJS	G/G	C/T	T/T	C/C	G/A	A/A	G/G	*4/*6A	IA
ST02	TEN	G/G	C/C	T/T	C/C	G/G	A/A	G/G	*4/*4	RA
ST03	SJS	G/G	C/T	T/T	C/C	G/G	A/A	G/A	*4/*7B	IA
ST04	SJS	G/G	C/T	T/T	C/C	G/A	A/A	G/G	*4/*6A	IA
ST05	SJS	G/G	C/C	T/T	C/C	G/G	A/A	G/G	*4/*4	RA
ST06	SJS	G/G	T/T	T/T	C/C	A/G	A/A	G/A	*6A/*7B	SA
ST07	SJS	G/G	C/C	T/C	C/T	G/G	A/G	G/G	*4/*5B	IA
ST08	SJS	G/G	C/T	T/T	C/C	A/G	A/A	G/G	*4/*6A	IA
D01	DIHS	G/G	T/T	T/T	C/C	A/A	A/A	G/G	*6A/*6A	SA
D02	DIHS	G/G	C/T	T/T	C/C	G/A	A/A	G/G	*4/*6A	IA
D03	DIHS	G/G	C/T	T/T	C/C	G/A	A/A	G/G	*4/*6A	IA
D04	DIHS	G/G	C/T	T/T	C/C	G/A	A/A	G/G	*4/*6A	IA
D05	DIHS	G/G	C/C	T/T	C/C	G/G	A/A	G/G	*4/*4	RA
D06	DIHS	G/G	T/C	T/T	C/C	G/G	A/G	A/G	*7B/*12A	IA
D07	DIHS	G/G	T/T	T/T	C/C	A/G	A/A	G/A	*6A/*7B	SA

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; IA, intermediate acetylator; RA, rapid acetylator; SA, slow acetylator; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[1]Alleles *4 and *12A were defined as RA alleles.

[2]Alleles *5B, *6A, and *7B were defined as SA alleles.

[3]Diplotypes comprised RA only, both RA and SA, and SA only, and they were defined as RA, IA, and SA phenotypes, respectively.

Supplementary Table S5. Association of *NAT2* Status with Sulfonamide-Related SJS or TEN and DIHS

NAT2	Control (N = 2,857)	SJS/TEN (N = 8)	DIHS (N = 7)	All SCAR (N = 15)
Allele				
RA allele[1]	3,951	9	6	15
SA allele[2]	1,763	7	8	15
OR		0.57	0.33	0.45
95% confidence interval		0.21−1.54	0.12−0.97	0.22−0.91
Fisher exact *P*		0.283	0.0430	0.0292
P corrected		0.849	0.129	0.087
RA + IA vs. SA (recessive model)[3]				
OR		0.71	0.25	0.41
95% confidence interval		0.09−5.81	0.05−1.32	0.11−1.45
Fisher's exact *P*		0.540	0.132	0.157
P corrected		1	0.396	0.471

Abbreviations: DIHS, drug-induced hypersensitivity syndrome; IA, intermediate acetylator; RA, rapid acetylator; SA, slow acetylator; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

[1]Genotypes **4* and **12A* were defined as RA alleles.

[2]Genotypes **5B*, **6A*, and **7B* were defined as SA alleles.

[3]Homozygous RA alleles, heterozygotes of RA and SA alleles, and homozygous SA alleles were defined as RA, IA, and SA phenotypes, respectively.