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Human Leukocyte Antigens and Sulfamethoxazole/Cotrimoxazole–Induced Severe Cutaneous Adverse Reactions
A Systematic Review and Meta-Analysis

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IMPORTANCE Sulfamethoxazole (SMX) and cotrimoxazole (CTX), a fixed-dose combination of SMX and trimethoprim in a 5:1 ratio, are antibacterial sulfonamides commonly used for treating various diseases. A substantial prevalence of severe cutaneous adverse reactions (SCARs) following the administration of these drugs has been reported. However, the association between human leukocyte antigen (HLA) genotypes and SMX/CTX-induced SCARs has remained unclear.

OBJECTIVE To investigate the association between HLA genotypes and SMX/CTX-induced SCARs.

DATA SOURCES A comprehensive search was conducted in CENTRAL (Cochrane Library), MEDLINE, and Embase from inception to January 17, 2023.

STUDY SELECTION Case-control studies that recruited patients who had experienced SCARs following SMX or CTX were included, and HLA alleles were analyzed.

DATA EXTRACTION AND SYNTHESIS Two independent authors extracted data on study characteristics and outcome data. The Meta-analysis of Observational Studies in Epidemiology (MOOSE) reporting guideline and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines were followed. The Newcastle-Ottawa Scale for case-control studies was used to assess study quality. Odds ratios (ORs) were calculated using a random-effects model for meta-analysis.

MAIN OUTCOMES AND MEASURES The prespecified outcome was the OR comparing SMX/CTX-induced SCARs with healthy or SMX/CTX-tolerant controls based on different HLA alleles.

RESULTS Six studies involving 322 patients with SCAR were included, including 236 patients with Stevens-Johnson syndrome/toxic epidermal necrolysis, 86 with drug reaction with eosinophilia and systemic symptoms, 8448 healthy controls, and 229 tolerant controls. Significant associations were found in *HLA-A*11:01* (OR, 2.10; 95% CI, 1.11-4.00), *HLA-B*13:01* (OR, 5.96; 95% CI, 1.58-22.56), *HLA-B*15:02* (OR, 2.23; 95% CI, 1.20-4.14), *HLA-B*38:02* (OR, 3.47; 95% CI, 1.42-8.48), and *HLA-C*08:01* (OR, 2.63; 95% CI, 1.07-6.44) compared with tolerant controls. In the Stevens-Johnson syndrome/toxic epidermal necrolysis subgroup, significant associations were found in *HLA-B*15:02* (OR, 3.01; 95% CI, 1.56-5.80) and *HLA-B*38:02* (OR, 5.13; 95% CI, 1.96-13.47). In the drug reaction with eosinophilia and systemic symptoms subgroup, significant associations were found in *HLA-A*68:01* (OR, 12.86; 95% CI, 1.09-151.34), *HLA-B*13:01* (OR, 23.09; 95% CI, 3.31-161.00), *HLA-B*39:01* (OR, 4.56; 95% CI, 1.31-15.82).

CONCLUSIONS AND RELEVANCE The results of this systematic review and meta-analysis suggest that multiple HLA alleles (*HLA-A*11:01*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:02*, and *HLA-C*0801*) are associated with SMX/CTX-induced SCARs.

Editor's Note page 534

Supplemental content

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Sulfamethoxazole (SMX) and cotrimoxazole (CTX), a fixed-dose combination of SMX and trimethoprim (TMP) in a 5:1 ratio, are broad-spectrum antibacterial sulfonamides widely used in managing bacterial, fungal, and protozoal infections.[1,2] Previous investigations have revealed a substantial prevalence of severe cutaneous adverse reactions (SCARs), encompassing Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), following the administration of SMX or CTX.[1-6] In most cases of CTX-induced SCARs, it is believed that SMX, rather than TMP, serves as the causative agent due to its capacity to activate T cells.[5] The direct involvement of human leukocyte antigens (HLAs), genes in the major histocompatibility complexes (MHC) playing a crucial role in distinguishing between self and nonself, has been proven in the pathogenesis of drug hypersensitivity.[7] Further studies highlighted the variability in the association between HLA alleles and drug hypersensitivity among different geographic populations.[8] For example, carbamazepine-induced SJS/TEN was specifically associated with *HLA-B*15:02* in the Han Chinese population.[8]

To date, evidence has demonstrated that specific HLA alleles are associated with SMX/CTX-induced SCARs. In East Asian populations, including Taiwanese, Thai, and Malaysian groups, the *HLA-B*13:01* and *HLA-B*15:02* alleles have shown significant associations with SMX/CTX-induced SCARs, particularly DRESS, while the *HLA-C*08:01* allele has been associated with SMX/CTX-induced SJS/TEN.[1,4-6] Among Japanese individuals, a significant association has been identified between the *HLA-A*11:01* allele and SMX-induced SCARs.[3] Conversely, in those with European descent, *HLA-B*38* has been predominantly associated with SMX-induced SJS/TEN.[2] In addition to the discrepancies observed in studies involving participants from various geographic regions, there is variability in the reported odds ratios (ORs) for SMX/CTX-induced SCARs compared with control groups. In light of these disparities, a comprehensive review is warranted to investigate the association between HLA and SMX/CTX-induced SCARs. Therefore, we performed this systematic review and meta-analysis to address this issue, with a particular emphasis on exploring variations in the association across different geographic populations.

Key Points

Question Is there an association between human leukocyte antigen (HLA) and sulfamethoxazole (SMX)/cotrimoxazole (CTX)–induced severe cutaneous adverse reactions (SCARs)?

Findings In this systematic review and meta-analysis of 6 studies involving 322 patients with SCARs, significant associations were identified between the *HLA-A*11:01*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:02*, and *HLA-C*08:01* genotypes and SMX/CTX-induced SCARs. The *HLA-B*15:02* and *HLA-B*38:02* genotypes were significantly associated with SMX/CTX-induced Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), while the *HLA-A*68:01* and *HLA-B*39:01* genotypes were associated with SMX/CTX-induced drug reaction with eosinophilia and systemic symptoms; the *HLA-B*13:01* allele showed an association with SMX/CTX-induced SJS/TEN and drug reaction with eosinophilia and systemic symptoms.

Meaning The results of this review suggest that multiple HLA alleles were associated with SMX/CTX-induced SCARs.

Methods

This meta-analysis was registered with PROSPERO (CRD42022384815) and performed in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines regarding evidence selection, quality assessment, evidence synthesis, and research reporting.[9,10] The types of eligible studies included case-control and cross-sectional studies. Two experienced reviewers (P-C.W. and I-I.H.) independently performed the literature search, data extraction, and quality assessment.[11,12] Any disagreement was resolved by consensus among the reviewers or referred to a third reviewer (W.H.-C.).[13]

Data Selection and Search

The following basic eligibility criteria for evidence selection were predefined: (1) studies including patients with SMX-induced SCARs and controls (either SMX-tolerant controls or the general population controls) and (2) studies reporting the ORs and 95% CIs of SCARs in individuals who carried different HLA alleles. SCARs were defined as SJS, TEN, DRESS, and acute generalized exanthematous pustulosis as diagnosed by internists, dermatologists, or allergologists or diagnosed using the Registry of Severe Cutaneous Adverse Reactions criteria. Based on the aforementioned criteria, the relevant terms, including *sulfamethoxazole*, *co-trimoxazole*, *human leukocyte antigen*, and *severe cutaneous adverse reactions* were used in the literature search conducted in free text, medical subject headings, and abbreviations. The keywords were combined using appropriate Boolean operators, and a primary search strategy was developed without limitations regarding language and published data. The primary search strategy involved a CENTRAL (Cochrane Library) search, which was adapted to MEDLINE and Embase (eTable 1 in Supplement 1). The final search was completed on January 17, 2023.

Study Selection

After potential studies were identified, 2 authors (P.W. and I.H.) excluded irrelevant studies by screening the title and abstract according to the following exclusion criteria: (1) studies recruiting patients without SMX or CTX use or patients who took SMX or CTX without developing SCARs, (2) studies without a control group, (3) studies without the analysis of HLA alleles, (4) review articles or case reports, and (5) gray literature that did not provide patient data. Disagreements between the 2 authors were resolved by the corresponding author (W.-H.C.). No language limitations were applied.

Data Extraction and Quality Assessment

The following data were extracted from the included studies: reference (author name and year of publication), geographic population, culprit drug, HLA allele, type of SCARs, controls

(tolerant or healthy controls), diagnostic criteria of cases, and controls. The primary outcomes were the prevalence of SCARs in individuals with different HLA alleles, including *HLA-A*11:01*, *HLA-B*07:05*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:01*, *HLA-B*38:02*, *HLA-C*03:04*, *HLA-C*04:06*, *HLA-C*07:27*, and *HLA-C*08:01*, compared with healthy controls, and the prevalence of SCARs in individuals with HLA alleles, including *HLA-A*11:01*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:02*, and *HLA-C*08:01*, compared with tolerant controls. The secondary outcomes were the prevalence of SCARs in individuals with all the other HLA alleles from the included studies compared with healthy or tolerant controls. In instances in which different studies used identical patient and control groups, we incorporated the data from the most recent publication year into our analysis to avoid duplication. We performed subgroup analyses according to different phenotypes of SCARs, including SJS/TEN and DRESS. The risk of bias in the selected studies was assessed using the Newcastle-Ottawa Scale for case-control studies, which consisted of 3 sections, including selection, comparability, and exposure, with a maximum score of 9 points.

Data Synthesis and Analysis

We conducted a meta-analysis in a random-effects model for quantitative synthesis. Dichotomous analysis was performed for crude estimates using ORs with 95% CIs. To assess the quality of the pooling results, this study evaluated the heterogeneity and small study effect; I^2 and the *P* value of Cochran Q were used to assess heterogeneity. High heterogeneity was defined as an I^2 value of greater than 50% or a *P* value of Cochran Q of less than .10 (a threshold for heterogeneity detection). If the number of the study was greater or equal to 10, a small study effect was illustrated using the funnel plot and assessed using the Egger test to guarantee a good performance.[14] The pooled results seemed to be associated with a small study effect when the *P* value of the Egger test was less than .05.

Results

The flow diagram for evidence selection is displayed in eFigure 1 in Supplement 1. In total, 202 studies were identified from 3 biomedical databases. Manual screening further showed that 9 studies were duplicates. Of the remaining 193 studies, 148 (76.7%) were excluded after the title, abstract, and article type were screened because they were not SMX/CTX-related SCAR (n = 98), or they were not reporting data of HLA (n = 50). Full-text article assessment was performed for the remaining 45 studies, which further excluded 26 review articles, 1 conference abstract, 5 case reports, and 7 studies that contained no outcome of interest. Finally, the data sources of the eligible studies were obtained from 6 studies. All studies were included in this study for qualitative analysis and quantitative synthesis.

Characteristics and Quality of the Included Studies

Table 1 presents the characteristics of the included studies. The 6 studies involved 322 patients with SCARs, including 236 patients with SJS/TEN, 86 patients with DRESS, 8448 healthy controls, and 229 tolerant controls. These patients and controls included a diverse range of geographic populations, including those of European descent, Japanese, Malaysian, Taiwanese, and Thai. Culprit drugs for SCARs included SMX (n = 31) and CTX (n = 291). HLA alleles presented in each study were outlined and analyzed according to HLA-A, HLA-B, and HLA-C. Most studies exhibited high quality in selection, comparability, and exposure sections, with a score of 7 or higher (eTable 2 in Supplement 1).

Analysis of the Association Between HLA and SMX/CTX-Induced SCARs Using Healthy Control Studies

The associations between individuals with SMX/CTX-induced SCARs and different HLA alleles are presented in **Figure 1**, **Table 2**, and eFigure 2 and eTable 3 in Supplement 1. Significant associations were found in the *HLA-A*11:01* (OR, 2.16; 95% CI, 1.26-3.69), *HLA-B*07:05* (OR, 2.86; 95% CI, 1.49-5.52), *HLA-B*13:01* (OR, 5.35; 95% CI, 3.36-8.50), *HLA-B*15:02* (OR, 1.87; 95% CI, 1.39-2.52), *HLA-B*38:01* (OR, 4.26; 95% CI, 1.43-12.71), *HLA-B*38:02* (OR, 3.21; 95% CI, 1.81-5.68), *HLA-C*03:04* (OR, 3.33; 95% CI, 2.27-4.89), *HLA-C*04:06* (OR, 3.28; 95% CI, 1.22-8.81), *HLA-C*07:27* (OR, 11.38; 95% CI, 1.98-65.37), and *HLA-C*08:01* (OR, 1.47; 95% CI, 1.02-2.11) compared with healthy controls. Heterogeneities varied among different HLA alleles, ranging from 0% to 59%.

Analysis of the Association Between HLA and SMX/CTX-Induced SCARs Using SMX/CTX-Tolerant Control Studies

The associations between patients with SMX/CTX-induced SCARs and different HLA alleles are presented in **Figure 2**, Table 2, and eTable 3 in Supplement 1. Significant associations were found in *HLA-A*11:01* (OR, 2.10; 95% CI, 1.11-4.00), *HLA-B*13:01* (OR, 5.96; 95% CI, 1.58-22.56), *HLA-B*15:02* (OR, 2.23; 95% CI, 1.20-4.14), *HLA-B*38:02* (OR, 3.47; 95% CI, 1.42-8.48), and *HLA-C*08:01* (OR, 2.63; 95% CI, 1.07-6.44) compared with tolerant controls. Heterogeneities varied among different HLA alleles, ranging from 0% to 85%.

Subgroup Analyses of SJS/TEN and DRESS Using Healthy and Tolerant Controls

Subgroup analyses by type of SCARs, including SJS/TEN and DRESS, are presented in Table 2 and eTables 4 and 5 in Supplement 1. In the SJS/TEN group, significant associations were found in *HLA-B*07:05* (OR, 2.80; 95% CI, 1.41-5.58), *HLA-B*13:01* (OR, 2.49; 95% CI, 1.74-3.58), *HLA-B*15:02* (OR, 3.09; 95% CI, 1.90-5.02), *HLA-B*38:01* (OR, 4.26; 95% CI, 1.43-12.71), *HLA-B*38:02* (OR, 4.56; 95% CI, 2.65-7.85), *HLA-C*04:06* (OR, 3.37; 95% CI, 1.16-9.78), *HLA-C*07:27* (OR, 9.25; 95% CI, 1.22-70.20), and *HLA-C*08:01* (OR, 1.66; 95% CI, 1.13-2.44) compared with healthy controls. Heterogeneities ranged from 0% to 55%. As for tolerant controls, significant associations were found in *HLA-B*15:02* (OR, 3.01; 95% CI, 1.56-5.80), and *HLA-B*38:02* (OR, 5.13; 95% CI, 1.96-13.47). No heterogeneities were observed in these 2 outcomes.

In the DRESS group, significant associations were found in *HLA-A*68:01* (OR, 7.03; 95% CI, 1.45-34.15), *HLA-B*13:01*

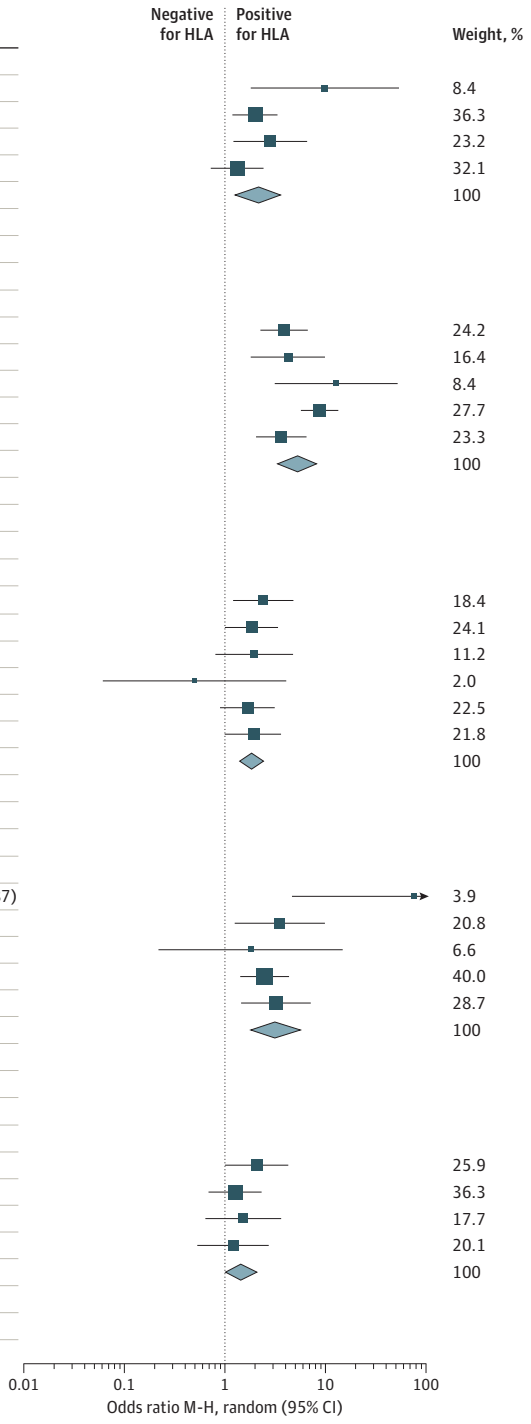
Table 1. Characteristics of Included Studies

Source	Geographic population (No.)	Culprit drug	HLA allele	Type of SCARs (No.)	Control (No.)	Diagnostic criteria	
						Cases	Controls
Loujou et al,[2] 2008	European	SMX	*HLA-B*38:01*, *HLA-B*38:02*, *HLA-B*38:11*	SJS/TEN (25)	Healthy (1822)	Patients who took CTX and developed SJS/TEN. SJS/TEN was diagnosed using RegiSCAR criteria.	NR
Kongpan et al,[6] 2015	Thai	CTX	*HLA-B*15:02*, *HLA-C*06:02*, *HLA-C*08:01*	SJS/TEN (43)	Tolerant (91); healthy (400)	Patients who took CTX and developed SJS/TEN. SJS/TEN was diagnosed according to clinical morphology of the skin lesions by internists or dermatologists. SJS was defined as skin detachment <10%; SJS/TEN overlap as 10%-30%; TEN as >30%.	Patients who took CTX >6 mo without evidence of SCARs; NR
Nakamura et al,[3] 2020	Japanese	SMX	*HLA-A*11:01*	SJS/TEN (5) and DIHS (n = 1)	Healthy (2878)	Patients who took SMX and developed SJS/TEN and DIHS.	NR
Sukasem et al,[1] 2020	Thai	CTX	*HLA-A*02:03*, *HLA-A*02:07*, *HLA-A*11:01*, *HLA-A*24:02*, *HLA-A*24:07*, *HLA-A*33:03*, *HLA-B*07:05*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:02*, *HLA-B*40:01*, *HLA-B*46:01*, *HLA-B*58:01*, *HLA-C*01:02*, *HLA-C*03:02*, *HLA-C*03:04*, *HLA-C*04:01*, *HLA-C*04:03*, *HLA-C*07:02*, *HLA-C*07:27*, *HLA-C*08:01*	SJS/TEN (18) and DRESS (12)	Tolerant (91); healthy (150)	Patients who took CTX and developed SJS/TEN and DRESS. SJS/TEN and DRESS were diagnosed using RegiSCAR criteria.	Patients who took CTX >6 mo without evidence of SCARs; NR
Wang et al,[5] 2021	Malaysian (8); Taiwanese (91); Thai (52)	CTX	*HLA-B*13:01*, *HLA-B*15:02*, *HLA-B*38:02*, *HLA-B*39:01*, *HLA-C*03:04*	SJS/TEN (94) and DRESS (57)	Tolerant (138); healthy (2545)	Patients who took CTX and developed SJS/TEN and DRESS. SJS/TEN and DRESS were diagnosed using RegiSCAR criteria.	Patients who took CTX >2.5 mo without evidence of SCARs.; NR
Nakkam et al,[4] 2022	Thai	CTX	*HLA-A*02:07*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-C*08:01*, *HLA-C*14:02*	SJS/TEN (51)	Tolerant (91); healthy (653)	Patients who took CTX and developed SJS/TEN. SJS/TEN was diagnosed according to clinical morphology of the skin lesions by internists or dermatologists. SJS was defined as skin detachment <10%; SJS/TEN overlap as 10%-30%; TEN as >30%.	Patients who took CTX >6 mo without evidence of SCARs; NR
			*HLA-A*68:01*, *HLA-B*13:01*, *HLA-C*03:04*	DRESS (16)			
			*HLA-A*02:07*, *HLA-A*11:01*, *HLA-B*07:05*, *HLA-B*13:01*, *HLA-B*15:02*, *HLA-C*04:06*, *HLA-C*08:01*, *HLA-C*14:02*	SJS/TEN (51) and DRESS (16)			

Abbreviations: CTX, cotrimoxazole; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; NR, no response; RegiSCAR, Registry of Severe Cutaneous Adverse Reactions; SCARs, severe cutaneous adverse reactions; SJS, Stevens-Johnson syndrome; SMX, sulfamethoxazole; TEN, toxic epidermal necrolysis.

Figure 1. Prevalence of Severe Cutaneous Adverse Reactions (SCARs) in Individuals Carrying Different Human Leukocyte Antigen (HLA) Alleles Compared With Healthy Controls

Study or subgroup	SCAR Events	SCAR Total	Healthy control Events	Healthy control Total	Odds ratio M-H, random (95% CI)	Weight, %
4.3.1 *HLA-A*11:01*						
Nakamura et al,[3] 2020	4	6	486	2878	9.84 (1.80-53.89)	8.4
Nakkam et al,[4] 2022	41	67	289	653	1.99 (1.19-3.32)	36.3
Sukasem et al,[1] 2020	21	30	68	150	2.81 (1.21-6.55)	23.2
Wang et al,[5] 2021 (Taiwan)	24	43	1245	2545	1.32 (0.72-2.42)	32.1
Subtotal (95% CI)		146		6226	2.16 (1.26-3.69)	100
Total events	90		2088			
Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 5.80$, df = 3 ($P = .12$); $I^2 = 48\%$						
Test for overall effect: $z = 2.82$ ($P = .01$)						
4.3.3 *HLA-B*13:01*						
Nakkam et al,[4] 2022	25	67	87	653	3.87 (2.25-6.67)	24.2
Sukasem et al,[1] 2020	13	30	23	150	4.22 (1.81-9.86)	16.4
Wang et al,[5] 2021 (Malaysia)	4	8	69	951	12.78 (3.13-52.22)	8.4
Wang et al,[5] 2021 (Taiwan)	48	91	289	2545	8.71 (5.67-13.39)	27.7
Wang et al,[5] 2021 (Thailand)	21	52	179	1135	3.62 (2.03-6.44)	23.3
Subtotal (95% CI)		248		5434	5.35 (3.36-8.50)	100
Total events	111		647			
Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 9.86$, df = 4 ($P = .04$); $I^2 = 59\%$						
Test for overall effect: $z = 7.09$ ($P < .001$)						
4.3.4 *HLA-B*15:02*						
Kongpan et al,[6] 2015	14	43	67	400	2.40 (1.20-4.78)	18.4
Nakkam et al,[4] 2022	16	67	95	653	1.84 (1.01-3.37)	24.1
Sukasem et al,[1] 2020	9	30	27	150	1.95 (0.81-4.73)	11.2
Wang et al,[5] 2021 (Malaysia)	1	8	212	951	0.50 (0.06-4.07)	2.0
Wang et al,[5] 2021 (Taiwan)	12	91	212	2545	1.67 (0.90-3.12)	22.5
Wang et al,[5] 2021 (Thailand)	14	52	183	1135	1.92 (1.02-3.61)	21.8
Subtotal (95% CI)		291		5434	1.87 (1.39-2.52)	100
Total events	66		796			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.18$, df = 5 ($P = .82$); $I^2 = 0\%$						
Test for overall effect: $z = 4.15$ ($P < .001$)						
4.3.6 *HLA-B*38:02*						
Loujou et al,[2] 2008	1	25	1	1822	75.88 (4.61-1248.87)	3.9
Sukasem et al,[1] 2020	7	30	12	150	3.50 (1.25-9.82)	20.8
Wang et al,[5] 2021 (Malysia)	1	8	70	951	1.80 (0.22-14.82)	6.6
Wang et al,[5] 2021 (Taiwan)	16	91	202	2545	2.47 (1.42-4.33)	40.0
Wang et al,[5] 2021 (Thailand)	8	52	61	1135	3.20 (1.44-7.10)	28.7
Subtotal (95% CI)		206		6603	3.21 (1.81-5.68)	100
Total events	33		346			
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 5.93$, df = 4 ($P = .20$); $I^2 = 33\%$						
Test for overall effect: $z = 3.99$ ($P < .001$)						
4.3.13 *HLA-C*08:01*						
Kongpan et al,[6] 2015	12	43	63	400	2.07 (1.01-4.25)	25.9
Nakkam et al,[4] 2022	15	67	122	653	1.26 (0.68-2.30)	36.3
Sukasem et al,[1] 2020	9	30	33	150	1.52 (0.64-3.63)	17.7
Wang et al,[5] 2021 (Taiwan)	7	43	354	2545	1.20 (0.53-2.73)	20.1
Subtotal (95% CI)		183		3748	1.47 (1.02-2.11)	100
Total events	43		572			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.37$, df = 3 ($P = .71$); $I^2 = 0\%$						
Test for overall effect: $z = 2.05$ ($P = .04$)						



Test for subgroup differences: $\chi^2 = 21.63$; df = 4 ($P < .001$); $I^2 = 81.5\%$.

(OR, 23.93; 95% CI, 12.69-45.15), *HLA-B*38:01* (OR, 4.26; 95% CI, 1.43-12.71), *HLA-B*39:01* (OR, 3.70; 95% CI, 1.64-8.35), *HLA-C*03:04* (OR, 3.93; 95% CI, 2.71-5.69), and *HLA-C*07:27* (OR, 14.80; 95% CI, 1.88-116.34) compared with healthy controls. Heterogeneities ranged from 0% to 21%. Regarding tolerant controls, significant associations were found in the *HLA-A*68:01* (OR, 12.86; 95% CI, 1.09-151.34), *HLA-B*13:01* (OR, 23.09; 95% CI, 3.31-161.00), and *HLA-B*39:01* (OR, 4.56; 95% CI, 1.31-15.82). A high heterogeneity (84%) was observed.

Table 2. Summary ORs of the Included Studies Categorized by Type of SCARs and Controls

Subgroup	Control	HLA allele	Study, No.	Effect size, OR (95% CI)	*P* value	I^2, %
SCAR	Healthy	*HLA-A*11:01*	4	2.16 (1.26-3.69)	.01	48
		*HLA-B*07:05*	3	2.86 (1.49-5.52)	.002	0
		*HLA-B*13:01*	5	5.35 (3.36-8.50)	<.001	59
		*HLA-B*15:02*	5	1.87 (1.39-2.52)	<.001	0
		*HLA-B*38:01*	1	4.26 (1.43-12.71)	NA	NA
		*HLA-B*38:02*	5	3.21 (1.81-5.68)	<.001	33
		*HLA-C*03:04*	2	3.33 (2.27-4.89)	<.001	0
		*HLA-C*04:06*	2	3.28 (1.22-8.81)	.02	0
		*HLA-C*07:27*	1	11.38 (1.98-65.37)	NA	NA
		*HLA-C*08:01*	4	1.47 (1.02-2.11)	.04	0
	Tolerant	*HLA-A*11:01*	1	2.10 (1.11-4.00)	NA	NA
		*HLA-B*13:01*	2	5.96 (1.58-22.56)	.01	85
		*HLA-B*15:02*	2	2.23 (1.20-4.14)	.01	0
		*HLA-B*38:02*	1	3.47 (1.42-8.48)	NA	NA
		*HLA-C*08:01*	1	2.63 (1.07-6.44)	NA	NA
SJS/TEN	Healthy	*HLA-B*07:05*	3	2.80 (1.41-5.58)	.003	0
		*HLA-B*13:01*	5	2.49 (1.74-3.58)	<.001	0
		*HLA-B*15:02*	6	3.09 (1.90-5.02)	<.001	55
		*HLA-B*38:01*	1	4.26 (1.43-12.71)	NA	NA
		*HLA-B*38:02*	5	4.56 (2.65-7.85)	<.001	16
		*HLA-C*04:06*	2	3.37 (1.16-9.78)	.03	0
		*HLA-C*07:27*	1	9.25 (1.22-70.20)	NA	NA
		*HLA-C*08:01*	4	1.66 (1.13-2.44)	.01	0
	Tolerant	*HLA-B*15:02*	2	3.01 (1.56-5.80)	.001	0
		*HLA-B*38:02*	1	5.13 (1.96-13.47)	NA	NA
DRESS	Healthy	*HLA-A*68:01*	1	7.03 (1.45-34.15)	NA	NA
		*HLA-B*13:01*	5	23.93 (12.69-45.15)	<.001	21
		*HLA-B*38:01*	1	4.26 (1.43-12.71)	NA	NA
		*HLA-B*39:01*	3	3.70 (1.64-8.35)	.002	0
		*HLA-C*03:04*	3	3.93 (2.71-5.69)	<.001	0
		*HLA-C*07:27*	1	14.80 (1.88-116.34)	NA	NA
	Tolerant	*HLA-A*68:01*	1	12.86 (1.09-151.34)	NA	NA
		*HLA-B*13:01*	2	23.09 (3.31-161.00)	.002	84
		*HLA-B*39:01*	1	4.56 (1.31-15.82)	NA	NA

Abbreviations: DRESS, drug reaction with eosinophilia and systemic symptoms; HLA, human leukocyte antigen; NA, not applicable; OR, odds ratio; SCAR, severe cutaneous adverse reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Subgroup Analyses of SCARs Using HIV-Positive Patients and Controls

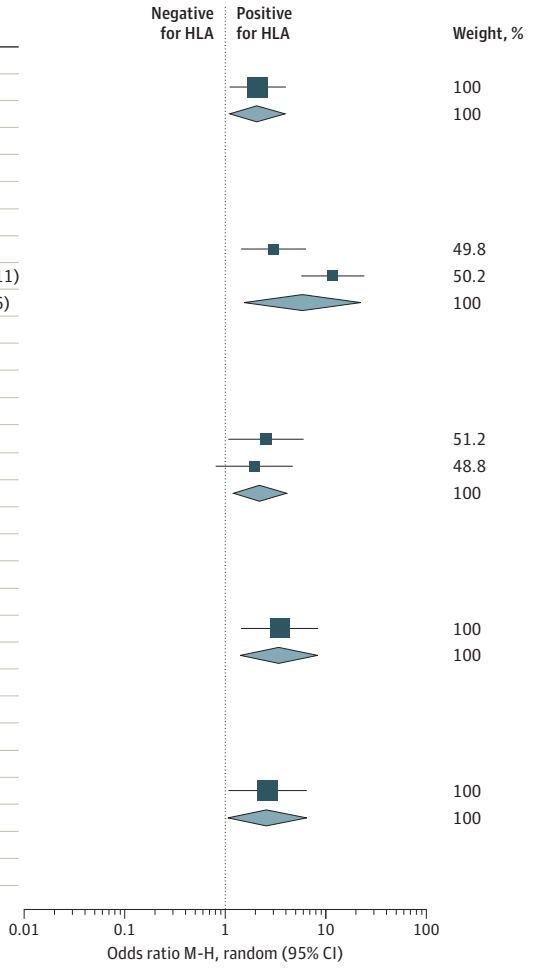
Subgroup analyses by type of SCARs, including SJS/TEN and DRESS, using HIV-positive patients and controls are presented in eTable 6 in Supplement 1. In the SCAR group, positive significant associations were found in *HLA-A*11:01* (OR, 2.43; 95% CI, 1.10-5.34), *HLA-B*07:05* (OR, 5.37; 95% CI, 1.17-24.70), *HLA-B*13:01* (OR, 2.61; 95% CI, 1.01-6.73), *HLA-B*15:02* (OR, 4.14; 95% CI, 1.44-11.86), *HLA-B*38:02* (OR, 4.90; 95% CI, 1.37-17.54), *HLA-C*07:27* (OR, 28.38; 95% CI, 1.46-550.96), and *HLA-C*08:01* (OR, 7.85; 95% CI, 2.08-29.62) compared with HIV-positive tolerant controls.

Subgroup Analyses of SCARs According to Different Geographic Populations

Subgroup analyses by different geographic populations are presented in eTable 7 in Supplement 1. In Thai populations, significant associations were found in *HLA-A*11:01* (OR, 2.10; 95% CI, 1.11-4.00), *HLA-B*13:01* (OR, 3.02; 95% CI, 1.43-6.34), *HLA-B*15:02* (OR, 2.54; 95% CI, 1.07-6.03), and *HLA-C*08:01* (OR, 2.63; 95% CI, 1.07-6.44) compared with tolerant controls. In the Taiwanese population, significant associations were found in *HLA-B*13:01* (OR, 11.72; 95% CI, 5.70-24.11) and *HLA-B*38:02* (OR, 3.47; 95% CI, 1.42-8.48) compared with tolerant controls. In those of European descent, significant associations were found in *HLA-B*38:01* (OR, 4.26; 95% CI, 1.43-12.71) and *HLA-B*38:02* (OR, 75.87; 95% CI, 4.61-1248.87) compared with healthy controls. In the Malaysian population, a significant association was found in *HLA-B*13:01* (OR, 12.78; 95% CI, 3.13-52.22) compared with healthy controls. In the Japanese population, a significant association was found in *HLA-A*11:01* (OR, 9.84; 95% CI, 1.80-53.89) compared with healthy controls.

Figure 2. Prevalence of Severe Cutaneous Adverse Reactions (SCARs) in Individuals Carrying Different Human Leukocyte Antigen (HLA) Alleles Compared With Tolerant Controls

Study or subgroup	SCAR Events	SCAR Total	Tolerant control Events	Tolerant control Total	Odds ratio M-H, random (95% CI)	Weight, %
4.2.2 *HLA-A*11:01*						
Nakamura et al,[3] 2022	41	67	39	91	2.10 (1.11-4.00)	100
Subtotal (95% CI)		67		91	2.10 (1.11-4.00)	100
Total events	41		39			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.26$ ($P = .02$)						
4.2.4 *HLA-B*13:01*						
Nakkam et al,[4] 2022	25	67	15	91	3.02 (1.43-6.34)	49.8
Wang et al,[5] 2021 (Taiwan)	48	91	12	138	11.72 (5.70-24.11)	50.2
Subtotal (95% CI)		158		229	5.96 (1.58-22.56)	100
Total events	73		27			
Heterogeneity: $\tau^2 = 0.78$; $\chi^2 = 6.61$, df = 1 ($P = .001$); $I^2 = 85\%$						
Test for overall effect: $z = 2.63$ ($P = .01$)						
4.2.5 *HLA-B*15:02*						
Nakkam et al,[4] 2022	16	67	10	91	2.54 (1.07-6.03)	51.2
Wang et al,[5] 2021 (Taiwan)	12	91	10	138	1.94 (0.80-4.71)	48.8
Subtotal (95% CI)		158		229	2.23 (1.20-4.14)	100
Total events	28		20			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.18$, df = 1 ($P = .67$); $I^2 = 0\%$						
Test for overall effect: $z = 2.54$ ($P = .01$)						
4.2.6 *HLA-B*38:02*						
Wang et al,[5] 2021 (Taiwan)	16	91	8	138	3.47 (1.42-8.48)	100
Subtotal (95% CI)		91		138	3.47 (1.42-8.48)	100
Total events	16		8			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.72$ ($P = .01$)						
4.2.9 *HLA-C*08:01*						
Nakkam et al,[4] 2022	15	67	9	91	2.63 (1.07-6.44)	100
Subtotal (95% CI)		67		91	2.63 (1.07-6.44)	100
Total events	15		9			
Heterogeneity: not applicable						
Test for overall effect: $z = 2.11$ ($P = .03$)						



Test for subgroup differences: $\chi^2 = 2.55$; df = 4 ($P = .64$); $I^2 = 0\%$.

Discussion

To our knowledge, this is the first systematic review and meta-analysis to explore the association between HLA and SMX/CTX-induced SCARs. Significant associations were identified between the *HLA-A*11:01*, *HLA-B*13:01, HLA-B*15:02, HLA-B*38:02,* and *HLA-C*08:01* genotypes and SMX/CTX-induced SCARs. A subgroup analysis in the SMX/CTX-induced SJS/TEN group demonstrated statistically significant associations in *HLA-B*15:02* and *HLA-B*38:02*, whereas *HLA-A*68:01* and *HLA-B*39:01* were significantly associated with SMX/CTX-induced DRESS. The *HLA-B*13:01* allele showed an association with SMX/CTX-induced SJS/TEN and DRESS, as evidenced by 3 studies involving Thai, Malaysian, and Taiwanese populations.[1,4,5] These significant associations were also observed in healthy controls.

SCARs are life-threatening conditions commonly associated with medications, and they can lead to mortality and severely debilitating complications.[5,15] Among the implicated drug classes, sulfonamide formulations containing compounds, such as SMX and CTX, characterized by the presence of an oxygen saturation–amines functional group, are frequently identified as causative agents of SCARs.[1-6] Sulfanilamide (SN), a principal metabolite of these compounds, exerts its antimicrobial function by inhibiting folate synthesis in bacterial organisms. However, the pathomechanism underlying SMX/CTX-induced SCARs remains debatable. Studies have proved that the sulfonamide moiety of SMX and CTX, along with its reactive metabolite 4-nitro SMX, are primary drug antigens responsible for hypersensitivity reactions.[5,16,17] Dapsone, another well-known sulfone drug used for treating infectious diseases and dermatoses, has also been associated with SCARs, particularly in patients carrying the *HLA-B*13:01* genotype.[3,18-20] In our study, we identified a significant association between the *HLA-B*13:01* genotype and SMX/CTX-induced SCARs in Asian populations, with an OR of 5.35 in healthy controls and 5.96 in tolerant controls. The *HLA-B*13:01* allele was associated with SMX/CTX-induced SJS/TEN and DRESS, as evidenced by 3 studies involving Thai, Ma-

laysian, and Taiwanese populations.[1,4,5] However, the ORs were much lower than those of dapsone-induced SCARs (OR, 43.0).[18] Dapsone and SMX share structural similarities; however, unlike SMX, dapsone does not produce SN during its metabolism.[3] Although docking models revealed that SMX and 4-nitro SMX bind to the same pocket in *HLA-B*13:01*, this binding pocket differs from that of dapsone.[21] However, results from an in vitro leukocyte activation test showed that patients with SMX/CTX-induced SCARs who possess the *HLA-B*13:01* allele exhibited a substantial cross-activity to dapsone (83%).[5] This cross-reactivity may help explain the varying ORs associated with *HLA-B*13:01* in the context of hypersensitivity reactions.

Our study had identified phenotype-specific genetic associations.[5] The *HLA-B*15:02* and *HLA-B*38:02* genotypes were associated with SMX/CTX-induced SJS/TEN, whereas the *HLA-A*68:01* and *HLA-B*39:01* genotypes were associated with SMX/CTX-induced DRESS. Similar phenotype-specific patterns have been reported in the context of carbamazepine-induced hypersensitivity reactions.[22,23] Although to our knowledge the precise mechanisms of these interactions have not been fully elucidated, it is conceivable that T-cell receptor (TCR) complexes play a role in the pathogenesis of severe hypersensitivity reactions.[24] In addition to *HLA-B*13:01*, the docking model also revealed that SMX could bind to *HLA-B*38:02*. Moreover, in patients possessing *HLA-DQB1*05:01* and *HLA-DQB1**02:01 who developed maculopapular exanthema, the activation of $CD4^+$ T cells specific to 4-nitro SMX was observed.[25] This finding suggests that SMX stimulation may be associated with HLA-DQ–restricted $CD4^+$ T-cell responses. Additionally, TCR containing Vβ20-1 may contribute to SMX-induced hypersensitivity, as confirmed by molecular dynamic modeling.[26] The potential immune interactions at the immune synapse between different HLA types and TCR may contribute to phenotype-specific associations in SMX/CTX-induced SCARs.

We conducted subgroup analyses of SCARs involving HIV-positive patients and controls from 3 Thai studies.[1,4,6] Compared with overall patients with SCARs, those with HIV-positive SCARs exhibited higher ORs for the *HLA-A*11:01*, *HLA-B*15:02*, *HLA-B*38:02*, and *HLA-C*08:01* alleles. Significant associations were found in the *HLA-B*07:05* and *HLA-C*07:27* alleles in HIV-positive patients with SCARs that were not observed in the overall SCAR patient group. According to demographic data from the 3 Thai studies, CTX was primarily used for the treatment or prevention of *Pneumocystis jirovecii* pneumonia infection in HIV-positive patients.[1,4,6] The increased frequency of HIV-positive patients in the SCAR case group may be attributed to the limitation on the use of CTX for treating infections other than *Pneumocystis jirovecii* pneumonia. Additionally, because 3 studies shared the same HIV-positive control group, we used data from the most recent and largest study by Nakkam et al[4] to avoid double counting. Information regarding CTX dosage in HIV-positive patients and controls was insufficient in these studies, and the association of dosage with the risk of SCAR development could not be evaluated.

We further conducted subgroup analyses based on different geographic populations. Significant associations were found in *HLA-B*13:01* across multiple geographic populations, including Malaysian, Taiwanese, and Thai populations. The *HLA-A*11:01* allele was significantly associated with SMX/CTX-induced SCARs in Japanese and Thai populations. Specific HLA alleles showed associations with specific geographic populations, such as *HLA-B*15:02* and *HLA-C*08:01* in Thailand, *HLA-B*38:02* in Taiwan, and *HLA-B*38:01* as well as *HLA-B*38:02* for those of European descent. These observed disparities in geographic distribution may be attributed to the complex nature of HLA allele involvement in the pathogenesis of SMX/CTX-induced SCARs. Similarly, carbamazepine, an antiepileptic medication frequently associated with SCARs, exhibited distinct preferences across different geographic populations. *HLA-B*15:02* and *HLA-A*31:01* were significantly associated with carbamazepine-induced SJS/TEN.[27-32] *HLA-B*15:02* showed a predominant association with higher risks among Han Chinese, Korean, Malaysian, and Thai populations,[27-30,33] while *HLA-A*31:01* was observed among European, Korean, and Japanese individuals.[29,31,32] The result suggests that multiple genetic factors may contribute to the pathogenesis of SMX/CTX-induced SCARs, and the underlying mechanisms may be more intricate compared with carbamazepine-induced reactions.

Limitations

In this systematic review, we expanded on the findings of individual articles by inclusively incorporating diverse geographic populations, such as those of European descent and Japanese, Malaysian, Taiwanese, and Thai individuals. Additionally, the study investigated associations through subgroup analyses based on different phenotypes, HIV status, and geographic populations. However, this study had several limitations. First, most included studies recruited patients from Southeast Asian countries. Further studies encompassing more diverse geographic populations are required. Second, there were 2 culprit drugs, SMX and CTX, for SCARs among the included studies.[1-6] Structural differences may contribute to the heterogeneities in some outcomes. Third, not all studies subcategorized SCARs into SJS/TEN and DRESS, and some studies did not include tolerant controls. Notably, in the studies conducted by Kongpan et al,[6] Sukasem et al,[1] and Nakkam et al,[4] tolerant control participants were derived from the same patient group. To prevent any potential issues of double counting, we used data exclusively from the most recent and largest study conducted by Nakkam et al[4] in our meta-analyses comparing patients with SMX/CTX-induced SCARs with tolerant controls. Fourth, sulfasalazine was not included in our meta-analysis. Although SMX and sulfasalazine release SN during metabolism, they still exhibit structural differences. Currently, to our knowledge only 1 study has investigated sulfasalazine-induced SCARs, which combined the results of SMX (n = 6) and sulfasalazine (n = 9) using the same control group.[3] To prevent double counting, we extracted the data for SMX from the study and integrated the results with data from other relevant studies. Finally, the significant associations found in the *HLA-A*11:01, HLA-B*15:02,* and *HLA-C*08:01* alleles may reflect the linkage disequilibrium in Asian populations. The frequency of the *HLA-A*11:01-B*15:02-C*08:01* haplotype was

approximately 8% in Kinh Vietnamese populations, while *HLA-A*11:01-B*15:02-C*08:01-DRB1*12:02-DQB1*03:01* was around 2% in Chinese populations.[34,35] Therefore, the results of our study should be interpreted more conservatively.

Conclusions

In this systematic review and meta-analysis, we identified significant associations between the *HLA-A*11:01*, *HLA-B*13:01, HLA-B*15:02, HLA-B*38:02,* and *HLA-C*08:01* genotypes and SMX/CTX-induced SCARs in SMX/CTX-tolerant and healthy control groups. Moreover, the *HLA-B*15:02* and *HLA-B*38:02* genotypes were significantly associated with SMX/CTX-induced SJS/TEN, while the *HLA-A*68:01* and *HLA-B*39:01* genotypes were associated with SMX/CTX-induced DRESS. The *HLA-B*13:01* allele showed an association with SMX-CTX-induced SJS/TEN and DRESS. Further studies that incorporate tolerant controls and a more diverse range of populations are warranted to enhance the broader applicability of the findings across different geographic regions.

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Editor's Note

Precision in Language Regarding Geographic Region of Origin in Severe Cutaneous Adverse Drug Reaction Research

Mya L. Roberson, PhD

In this issue of *JAMA Dermatology*, Wu et al[1] conducted a systematic review and meta-analysis of studies assessing the association between human leukocyte antigens and sulfamethoxazole/cotrimoxazole–induced severe cutaneous adverse reactions. In this study, the authors reported a subgroup analysis of severe cutaneous adverse reactions by geographic region of origin inclusive of Japanese, Malaysian, Taiwanese, Thai, and European individuals. The level of granularity in analysis and reporting conducted by Wu et al[1] on the geographic region of origin of patients is an important reminder of the genetic and clinical variation that can exist within populations that are often racialized into large heterogeneous groups.

Related article page 525

Race and ethnicity are sociopolitical constructs that can vary by time and geography and are frequently used for the social stratification of groups.[2] These constructs have had an evolving role in medical and dermatological research over the course of time.[3] Specifically in the context of drug-induced severe cutaneous adverse reactions, such as Stevens-Johnson syndrome/toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms, there can exist a tension in the accurate reporting of the epidemiology of these conditions and their association with human leukocyte antigens among various racial and ethnic groups. Given existing within-group genetic heterogeneity among various racial and ethnic groups, capturing and reporting geographic region of origin at its most granular level becomes paramount. Precision in measurement and reporting of nationality in such investigations rejects the notion of biological essentialism and promotes the understanding and potential identification of patients at greatest risk.

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