

Original Article



The Fas Signaling Pathway Is a Common Genetic Risk Factor for Severe Cutaneous Drug Adverse Reactions Across Diverse Drugs

Heung-Woo Park ,^{1,2*} Sang-Heon Kim,³ Yoon-Seok Chang,⁴ Sang-Hoon Kim,⁵ Young-Koo Jee,⁶ Ai-Young Lee,⁷ In-Jin Jang,⁸ Hae-Sim Park ,⁹ Kyung-Up Min^{1,2}

¹Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

²Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea

³Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea

⁴Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

⁵Department of Internal Medicine, Eulji University School of Medicine, Daejeon, Korea

⁶Department of Internal Medicine, Dankook University College of Medicine, Cheonan, Korea

⁷Department of Dermatology, Dongguk University Ilsan Hospital, Goyang, Korea

⁸Department of Clinical Pharmacology and Therapeutics, Seoul National University College of Medicine, Seoul, Korea

⁹Department of Allergy and Clinical Immunology, Ajou University School of Medicine, Suwon, Korea



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Correspondence to

Heung-Woo Park, MD, PhD

Department of Internal Medicine, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 03080, Korea.

Tel: +82-2-2072-0699

Fax: +82-2-742-3291

E-mail: guinea71@snu.ac.kr

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ORCID iDs

Heung-Woo Park

<https://orcid.org/0000-0002-6970-3228>

Hae-Sim Park

<https://orcid.org/0000-0003-2614-0303>

ABSTRACT

Purpose: Human leukocyte antigen (HLA) has been recognized as the most important genetic risk factor for severe cutaneous adverse drug reactions (SCARs) caused by certain drugs. However, cumulated observations suggest the presence of genetic risk factors for SCARs other than drug-specific HLA. We aimed to identify a common genetic risk factor of SCARs across multiple drugs.

Methods: We performed 2 independent genome-wide association studies (GWASs). A total of 68 and 38 subjects with a diagnosis of SCAR were enrolled in each GWAS. Their allele frequencies were compared to those of healthy subjects in Korea.

Results: No single nucleotide polymorphism (SNP) with genome-wide significance was found in either GWAS. We next selected and annotated the 200 top-ranked SNPs from each GWAS. These 2 sets of annotated genes were then entered into the web interface of *ConsensusPathDB* for a pathway-level analysis. The Fas signaling pathway was significantly over-represented in each gene set from the 2 GWASs.

Conclusions: Our observations suggest that the Fas signaling pathway may be a common genetic risk factor for SCARs across multiple drugs.

Keywords: Drug; Stevens-Johnson syndrome; toxic epidermal necrolysis; genome-wide association study; Fas signaling pathway

INTRODUCTION

Severe cutaneous adverse drug reactions (SCARs) characterized by an acute inflammatory reaction of the skin and mucous membranes are very rare, but sometimes fatal.¹ SCARs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash

Disclosure

There are no financial or other issues that might lead to conflict of interest.

with eosinophilia and systemic symptoms (DRESS).¹ Thus far, human leukocyte antigen (HLA) has been recognized as the most important genetic risk factor for SCARs caused by certain drugs.² However, we reported that only 20% of carriers of the HLA-B*58:01 allele experienced an allopurinol-induced SCAR.³ Similarly, the risk of carbamazepine-induced hypersensitivity was 26% in carriers of HLA-A*31:01 in a European population.⁴ These observations suggest the presence of genetic risk factors for SCARs other than drug-specific HLA. The purpose of this study was to identify common genetic risk factors of SCARs in addition to drug-specific HLA. Cases of SCAR induced by various drugs were collected and a genome-wide association study (GWAS) was performed. As previously mentioned, drug-specific HLA is believed to be the strongest risk factor for SCAR. Therefore, it is possible that genetic variants with modest effects on SCAR are not captured in a GWAS. To overcome this problem, we used the gene set-based approach, which increases the likelihood of identifying the biological pathway involved by utilizing enrichment tools.⁵

MATERIALS AND METHODS

We performed 2 independent GWASs in 2008 (the first) and 2012 (the second). All subjects with SCAR were enrolled by the Adverse Drug Reaction Research Group, Korea. Each study was approved by the Institutional Review Board of the Seoul National University Hospital (H-0506-150-011 and C-1111-100-387) and informed consent was obtained from all study participants.

Study subjects and phenotype definitions

SJS, SJS/TEN overlap and TEN were diagnosed according to the range of detached surface area (< 10%, 10%–30% and > 30%, respectively).^{6,7} DRESS was defined when a subject met at least five of the following criteria: development of a maculopapular rash more than 3 weeks after starting a limited number of drugs, prolonged clinical symptoms for 2 weeks after discontinuation of the causative drug, fever (> 38°C), liver abnormalities or other organ involvement, leukocyte abnormalities such as leukocytosis ($>11 \times 10^9$ cells/L), atypical lymphocytosis (> 5%), or eosinophilia ($>1.5 \times 10^9$ cells/L), lymphadenopathy, and human herpes virus 6 reactivation.⁸ All clinical evaluations were performed by allergy specialists with more than 10 years of experience in drug allergy consultation. A drug was classified as a cause of SCAR when it satisfied the grade of ‘certain’ or ‘probable’ on the World Health Organization-Uppsala Monitoring Center causality assessment system.⁹ Characteristics of subjects with SCAR are shown in **Table 1**. Control subjects were selected from a publicly available database to provide a 4:1 match with the case subjects. All control subjects were healthy Koreans and were genotyped on the same chip in each GWAS.

Genotyping

DNA of subjects included in the first GWAS was genotyped on the Affymetrix 500K Chip (Affymetrix, Santa Clara, CA, USA). DNA of subjects included in the second GWAS was genotyped on the Affymetrix Axiom[®] Genome-Wide East Asian Ancestry Chip. All single nucleotide polymorphisms (SNPs) that were included in the GWAS had a completion rate of >95%, a minor allele frequency of >0.05, and a Hardy-Weinberg equilibrium *P* value >0.0001.

Table 1. Characteristics of SCAR subjects

Characteristic	First GWAS (n = 68)	Second GWAS (n = 38)
Male	35 (51.5)	35 (51.5)
Age (yr)	49.8 ± 16.8	52 ± 19.2
Phenotype		
SJS/Overlap*/TEN/DRESS	14 (20.6)/12 (17.6)/4 (5.9)/38 (55.9)	7 (18.4)/6 (15.8)/4 (10.5)/21 (55.3)
Causative drug		
Allopurinol	13 (19.1)	5 (13.2)
Carbamazepine	18 (26.5)	3 (7.9)
Anti-epileptics except carbamazepine	7 (10.3) [†]	6 (15.8) [‡]
Acetaminophen	3 (4.4)	3 (7.9)
NSAID	6 (8.8) [‡]	12 (31.5) ^{**}
Beta-lactam antibiotics	7 (10.3) [§]	9 (23.7) ^{††}
Others	14 (20.6)	-

Data are shown as number (%) or mean ± standard deviation.

SCAR, severe cutaneous adverse drug reaction; GWAS, genome-wide association study; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; DRESS, drug rash with eosinophilia and systemic symptom; NSAID, non-steroidal anti-inflammatory drug.

*SJS/TEN overlap syndrome; [†]Including phenytoin (3), valproic acid (2), and lamotrigine (2); [‡]Including ibuprofen (4) and mefenamic acid (2); [§]Including ceftazidime (2), cefaclor (2), piperacillin (1), cefazolin (1), and cefpiramide (1); ^{||}Including anti-tuberculosis medication (6), oriental herbal medication (3), vancomycin (2), sulfasalazine (1), pantoprazole (1), and propylthiouracil (1); [†]Including phenytoin (5) and lamotrigine (1); ^{**}Including ibuprofen (6), loxoprofen (3), and mefenamic acid (3); ^{††}Including amoxicillin (2), cefaclor (2), cefbuparazone (1), cefixime (1), cefoxitin (1), cephradine (1), and meropenem (1).

Statistical analysis

Associations between SNPs and the occurrence of SCAR were measured according to a linear regression model, as implemented in PLINK,¹⁰ using an additive genetic model. The regression models were adjusted for age and sex. SNPs with P values $< 10^{-8}$ in the GWAS were considered genome-wide significant. For over-representation analysis, we selected and annotated the 200 top-ranked SNPs from both GWASs using the open-source software package *NCBI2R* in the statistical and graphical environment of R software (<http://www.r-project.org>). Only genes that harbored the SNP of interest were selected; 62 genes were identified from the first GWAS and 69 were identified from the second GWAS. Gene lists are provided in **Supplementary Tables S1** and **S2**. The list of genes was then entered into the web interface of *ConsensusPathDB* (<http://cpdb.molgen.mpg.de>) for pathway-level interpretation. *ConsensusPathDB* is a meta-database that integrates different types of functional interactions from heterogeneous interaction data resources.¹¹ To control for multiple tests, 0.05 was set as the limit of Q values, which were calculated using the false discovery rate method.

RESULTS

The top-ranked SNP in the first GWAS was rs2327661 ($P = 6.3 \times 10^{-7}$) and that in the second GWAS was rs8180036 ($P = 4.48 \times 10^{-6}$). However, none of the SNP reached genome-wide significance. A list of the 200 top-ranked SNPs is provided in **Supplementary Table S3** and the Manhattan plots each GWAS are presented in **Supplementary Fig. S1**. Over-representation analysis of the annotated gene sets by *ConsensusPathDB* identified 17 significant pathways in the first GWAS and 3 significant pathways in the second GWAS, see **Tables 2** and **3**. Interestingly, the Fas signaling pathway (the fourth ranked pathway in the first GWAS and the 1st ranked pathway in the second GWAS) was commonly found. Two genes (*CASP10* and *MAP3K7*) in the gene set from the first GWAS and 3 genes (*PTPN13*, *PRKDC* and *FADD*) in the gene set from the second GWAS were significantly over-represented in the Fas signaling pathway, see **Supplementary Table S4**.

Table 2. Pathway-based gene sets identified from the first GWAS

P value	Q value	Pathway	Source	Overlapped genes*
0.00069918	0.02407312	Propanoate metabolism	SMPDB	ACACA; ABAT
0.00091873	0.02407312	IL-4 signaling pathway	PID, BioCarta	HLA-DRA; JAK1
0.00109038	0.02407312	Leishmaniasis - Homo sapiens (human)	KEGG	HLA-DRA; MAP3K7; JAK1
0.00144439	0.02407312	Fas signaling pathway (cd95)	PID, BioCarta	CASP10; MAP3K7
0.00244457	0.02575628	A tetrasaccharide linker sequence is required for GAG synthesis	Reactome	VCAN; GPC5
0.00263548	0.02575628	Alk in cardiac myocytes	PID, BioCarta	BMP7; MAP3K7
0.00283319	0.02575628	Thrombin signaling and protease-activated receptors	PID, BioCarta	PLCB1; MAP3K7
0.00346684	0.02636741	IL-17 signaling pathway	Wikipathways	MAP3K7; JAK1
0.00346684	0.02636741	Mucin type O-glycan biosynthesis - Homo sapiens (human)	KEGG	GALNTL6; WBSCR17
0.00369144	0.02636741	Propanoate metabolism - Homo sapiens (human)	KEGG	ACACA; ABAT
0.00446835	0.02978898	Toxoplasmosis - Homo sapiens (human)	KEGG	HLA-DRA; MAP3K7; JAK1
0.00517687	0.03235546	FAS pathway and stress induction of HSP regulation	Wikipathways	CASP10; MAP3K7
0.00600657	0.03533279	BMP receptor signaling	PID	BMP7; MAP3K7
0.00751491	0.0417495	Proton pump inhibitor pathway, Pharmacodynamics	PharmGKB	PLCB1; AKAP2
0.00816134	0.04295442	Chondroitin sulfate/dermatan sulfate metabolism	Reactome	VCAN; GPC5
0.00917629	0.04588144	Downstream TCR signaling	Reactome	HLA-DRA; MAP3K7
0.00966203	0.04600966	Hippo signaling pathway - Homo sapiens (human)	KEGG	BMP7; GLI2; CTNNA3

Input options: 13 databases, minimum overlap with input list = 2 and P value cutoff = 0.01. Bold styled value means overlapped pathway.

GWAS, genome-wide association study.

*Overlapped genes between the input and database sets; bold denotes a common pathway identified from the first and second GWASs.

Table 3. Pathway-based gene sets identified from the second GWAS

P value	Q value	Pathway	Source	Overlapped genes*
0.00010214	0.00423877	Fas signaling pathway (cd95)	PID, BioCarta	PTPN13; FADD; PRKDC
0.00085642	0.02369427	G protein signaling pathways	Wikipathways	PRKCH; PDE4B; PRKAR2B; PDE8B
0.00214336	0.03557973	Repression of pain sensation by the transcriptional regulator, DREAM	PID, BioCarta	PRKAR2B; CREM

Input options: 13 databases, minimum overlap with input list = 2 and P value cutoff = 0.01. Bold styled value means overlapped pathway.

GWAS, genome-wide association study

*Overlapped genes between the input and database sets; bold denotes a common pathway identified from the first and second GWASs.

DISCUSSION

Previous GWASs have identified only SNPs located in the HLA region¹² or SNPs in linkage disequilibrium with HLA alleles^{13,14} as genetic risk factors for SCAR. In our study, causative drugs were diverse, and thus we could not adjust for the potential effects of the drug-specific HLA. Considering that the drug-specific HLA is believed to be the strongest genetic risk factor of SCAR, failure to adjust for its effects may partly explain why we did not detect any SNPs with genome-wide significance. It may be true that no single genetic variant confers an increased risk of SCAR greater than the drug-specific HLA. A gene set-based approach is widely used in genetic studies and has shown promising results. Likewise, we found that the gene sets annotated with the 200 top-ranked SNPs from t2 independent GWASs of SCAR induced by diverse drugs were commonly over-represented in the Fas signaling pathway. To the best of our knowledge, this is the first study to show that the Fas signaling pathway is a common genetic risk factor for SCAR across diverse drugs.

Over-representation analysis statistically evaluates the fraction of genes in a particular pathway found among a set of genes (input).⁵ Over-representation analysis can be performed in *ConsensusPathDB* using gene sets and functional modules derived from incorporating pathway definitions provided by the source databases. For each predefined module, a P value is calculated based on the hypergeometric distribution, which reflects the significance of the observed overlap between the input gene list and the module's members compared to random expectations.¹⁵ If the input list is obtained from a case-control study, over-representation analysis may indicate pathways and functional sub-networks that are dysregulated in the disease state.

The Fas receptor (CD95) mediates apoptosis via the Fas-ligand (FasL), which is expressed on the surface of other cells. The Fas-FasL interaction plays an important role in the immune system and a lack of this interaction leads to autoimmunity.¹⁶ Fas-induced keratinocyte apoptosis plays a key role in the pathogenesis of SCAR.^{17,18} Therefore, our observations suggest that the genetic susceptibility associated with the Fas signaling pathway may be a common (drug-non-specific) risk factor for the development of SCAR in conjunction with the drug-specific HLA, although detailed genetic mechanisms should be investigated in a future study.

Although genome-wide significance was not reached, some SNPs mapped to *NKAIN2* (Sodium/Potassium Transporting ATPase Interacting 2 gene) and *ANGPT2* (Angiopoietin 2 gene) showed significant associations with SCAR both in 2 GWASs. *NKAIN2* gene encodes a transmembrane protein that interacts with the beta subunit of a sodium/potassium-transporting ATPase. A previous report showed that a chromosomal translocation involving this gene was a cause of lymphoma.¹⁹ Angiopoietin 2 encoded by *ANGPT2* is an antagonist of angiopoietin 1 and thus disrupts its vascular remodeling ability which may induce endothelial cell apoptosis.²⁰ However, so far, there has been no report to show the association between SCAR or drug adverse reaction and *NKAIN2* or *ANGPT2*. This finding may emphasize an importance of the gene-set based analysis, although further mechanistic studies need to be performed.

There are a few limitations to the present study. First, our genotyping platforms differed between the 2 GWASs and thus SNPs genotyped overlapped poorly, which increased the likelihood that SNPs that were significantly associated with SCAR were not genotyped across the studies. However, it is known that the probabilistic nature of imputed SNPs presents challenges when testing for association of those SNPs.²¹ Therefore, we used a gene-based approach instead of imputation of our SNP dataset. Secondly, a SNP was annotated to a gene when a gene harbored that SNP within its chromosomal region. A SNP located outside of a gene can be functionally relevant by affecting the expression of genes located adjacently or remotely.²² In addition, we selected only the 200 top-ranked SNPs for analysis. Therefore, it is possible that some functionally important genes were missed and thus not included in the over-representation analysis, which limited the identification of more significant pathways. Secondly, approximately half of the enrolled subjects (subjects with a diagnosis of DRESS) showed skin eruption rather than blister or detachment. The role of Fas-FasL in the pathogenesis of drug eruption is not clear. However, a previous report showed that overlapping expression of Fas and FasL is accompanied by apoptosis in fixed-drug eruption lesions.²³ In addition, we found no difference between DRESS cases and all other cases in our over-representation analysis (data not shown). Thus, it is possible that the Fas signaling pathway plays its own role in the pathogenesis of eruption seen in subjects with DRESS. Another possible explanation is that prompt and intensive treatment may have stopped the progression from eruption to blister or detachment in the subjects enrolled in this study. Thirdly, a small number of patients with SCAR was also an important issue before generalizing our results. However, given that SCAR is a very rare event, our findings may provide investigators to prioritize variants for follow-up analysis. A pathway analysis based on the gene set is known to be particularly useful for pilot studies with small sample sizes.²⁴

In conclusion, an over-representation analysis using gene sets from 2 independent GWASs of SCAR induced by diverse drugs identified the Fas signaling pathway as a significant and common pathway. Our observations suggest that the Fas signaling pathway may be a common genetic risk factor for SCARs across diverse drugs.

SUPPLEMENTARY MATERIALS

Supplementary Table S1

A total of 62 SNPs and their annotated genes in the first GWAS used for an over-representation analysis

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Supplementary Table S2

A total of 69 SNPs and their annotated genes in the second GWAS used for an over-representation analysis

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Supplementary Table S3

The top-ranked 200 SNPs identified from the first and second GWAS

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Supplementary Table S4

Genes significantly over-represented in the Fas signaling pathway

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Supplementary Fig. S1

The Manhattan plots of each GWAS. (A) The first GWAS. (B) The second GWAS.

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