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CURRENT TOPIC

Pharmacogenomics for Treatment Response in Patients With Stevens-Johnson Syndrome: An Updated Review

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Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dermatological emergencies characterised by widespread epidermal necrolysis and sloughing. SJS is defined as the shedding of skin on less than 10 % of the body surface area, whereas TEN involves the shedding of skin on more than 30 %. The pathogenesis of SJS is identified by the occurrence of apoptosis of keratinocytes, which is spread throughout the body. The binding of the molecule to the *human leukocyte antigen (HLA)* peptide is one of the basic triggering mechanisms for SJS due to an autoimmune reaction. This study aims to predict genetic predictive markers for the prevention and pharmacological treatments of SJS/TEN. The *PharmGKB* website was used to gather information regarding the relationship among drugs, genes and the SJS condition. Results revealed notable gene variants (eg *HLA-A, HLA-B, HLA-B, HLA-C, CYP2B6*) predisposing individuals to a toxic response, instigating the SJS reaction. Implicated drugs included allopurinol, antiepileptics such as carbamazepine, lamotrigine, oxcarbazepine and phenytoin, as well as methazolamide and nevirapine, identified as potential risk factors. As a result, this study can provide information and facilitate precision medicine, which focuses on individual genetic variations as a means of prevention and treatment, enabling early prognosis and optimising patient care in preventing SJS/TEN.

Key words: Stevens-Johnson syndrome; Toxic epidermal necrolysis; Pharmacogenetics; Computational biology.

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Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dermatological emergencies characterised by widespread epidermal necrolysis and sloughing.[1, 2] The pathophysiology of these disorders is similar and they are categorised based on the body surface area (BSA) involved.[3] SJS is a mucocutaneous immunological reaction that can be fatal and is primarily brought on by medication consumption.[4, 5] Both SJS and TEN are immune-mediated mucocutaneous disorders that cause mucosal surfaces and severe skin exfoliation.[6, 7]

Skin loss on less than 10 % of the body's surface area is referred to as SJS, whereas skin loss on more than 30 % of the body is referred to as TEN. Ten percent to 30 % skin shedding is considered overlap between SJS and TEN.[8, 9] According to Korea's National Health Insurance database, the incidence of SJS in adults ranges from 3.96 to 5.3/1,000,000 while the incidence of TEN in the same group ranges from 0.4 to 1.45/1,000,000.[10] In SJS/TEN, severe skin sloughing can result in a high risk of morbidity and death. Patients with SJS and TEN have reported death rates of 4.8 % and 14.8 %, respectively.[11, 12] Early detection, diagnosis and appropriate pharmacological treatments can save lives for patients with SJS and TEN.[13, 14]

SJS pharmacogenetic problems can be observed in drug hypersensitivity reactions that occur in each individual. The objective of this study was to identify possible genetic predictive markers for the SJS/TEN prevention and pharmacological treatment.[12, 15] The pathogenesis of SJS involves the spread of apoptotic keratinocytes throughout the body.[16] The binding of the molecule to *human leukocyte antigen (HLA)* peptide is one of the basic triggering mechanisms for SJS due to an autoimmune reaction. Pharmacological agents, such as drugs, affect the processing of antigen-presenting cells and bind to specific *HLA* molecules or T-cell receptors that produce an immune response.[17] The early SJS phase stimulates cytotoxic CD^{8+} natural killer (NKT) T cells and NK cells to release molecules that lead to keratinocyte apoptosis, such as granulysin.[18]

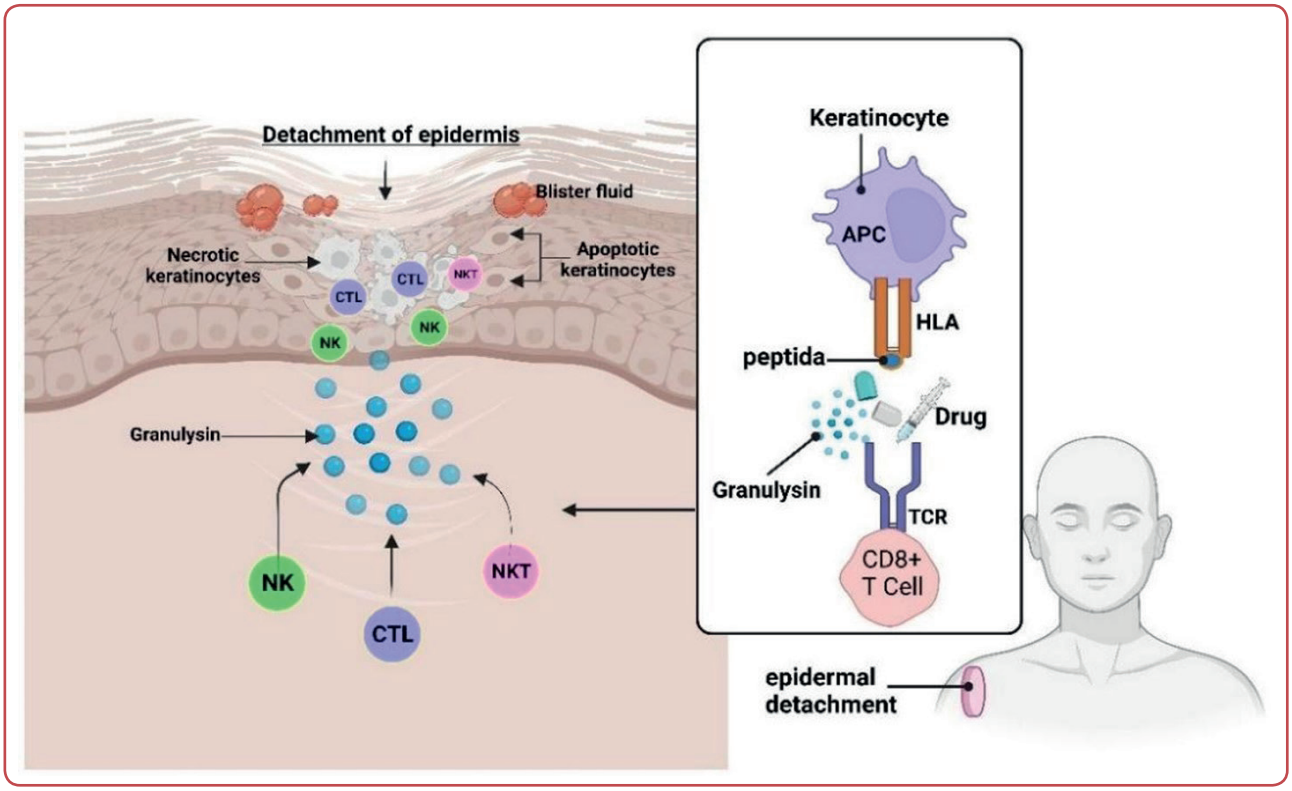

Figure 1: Illustration of how peptide antigens (from drugs in this case), keratinocytes, undergo a cytotoxic inflammatory response resulting in granulysin release, apoptosis and necrosis of keratinocytes, detachment of the epidermis and blister formation in Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The figure was created with BioRender.com under agreement number "OV25JPFML7".

Granulysin is a cytotoxic molecule commonly found in severe SJS blisters, may mediate T-cell induced cytotoxicity keratinocytes apoptosis through various apoptotic pathway components.[19] Cytotoxic mediators, such as TNF-alpha upregulate FasL, have been associated with keratinocyte apoptosis.[20] Keratinocyte apoptosis separates the epidermal from the dermis, resulting in the typical SJS/TEN skin shedding. As the cells die and necrosis, an increased antigen load triggers T cells to continue the inflammatory response with the appearance of fluid-filled blisters (Figure 1).[21]

Methods

Information by searching for data on genetic factors that cause SJS/TEN on the *PharmGKB* website was collected to build knowledge about the relationship between drugs, genes and disease.[22] Detailed information regarding the research design is depicted in Figure 2. The first step was to carry out identification using *PharmGKB* website (https://www.pharmgkb.org/), on 25 May 2023 and entering the search query "Stevens-Johnson Syndrome (SJS)" into the designated search field. The six tiers, numbered 1A through 4, stand for high, moderate and low to unsupported evidence, respectively, according to *PharmGKB*. Drug data were collected using criterion levels 1A through 2B.[23]

The second step of the analysis proceeded to the clinic annotations section. This phase involved extracting valuable insights related to the study of drug variants and phenotypic categories, with adjustments made based on the level of supporting evidence. The level of evidence (LOE) for each variant was determined using the *PharmGKB* database, which involves annotating variants and considering various factors such as phenotype, p-value, cohort size, effect size and study type.[24] A meticulous examination of variant annotations followed, shedding light on the intricate relationships between genetic variants and drug-related phenotypes, drawing from literature publications

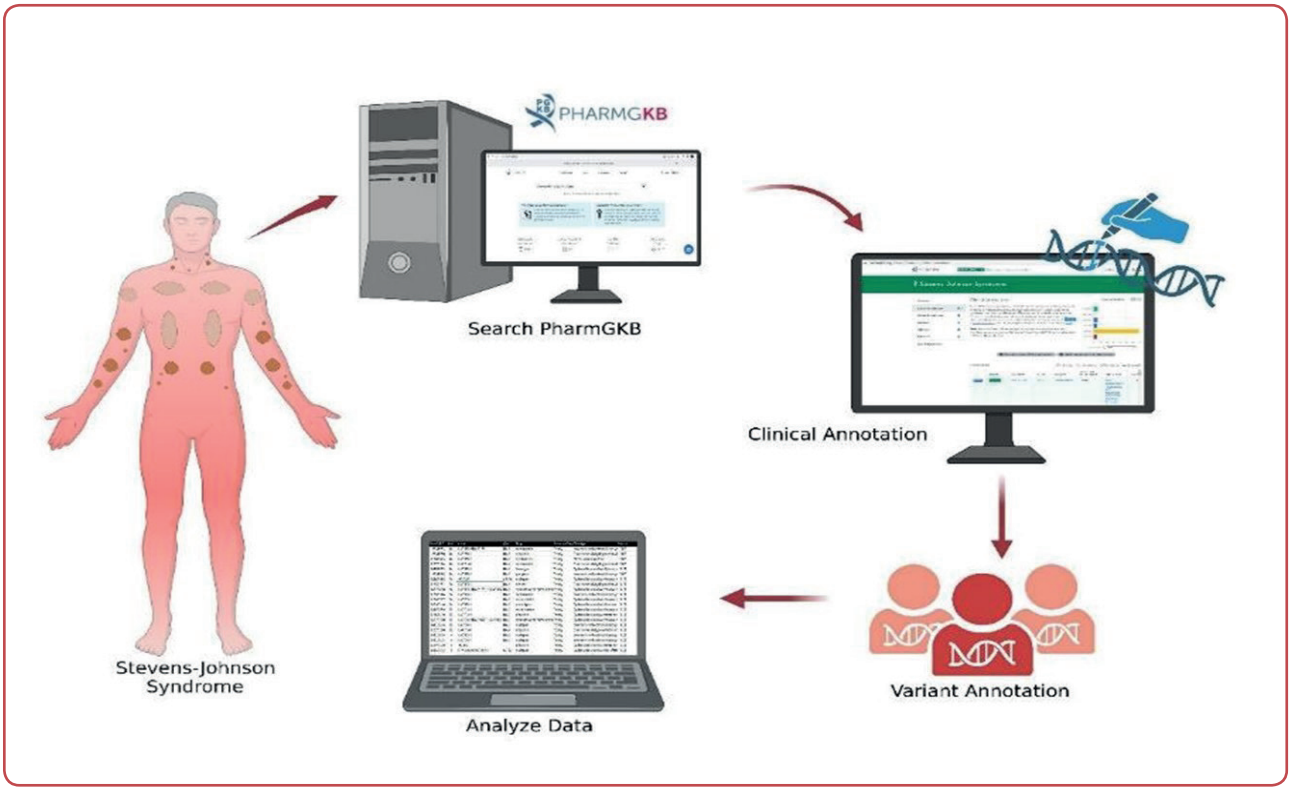

Figure 2: Schematic illustration of the identification of genetic variants associated with Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The figure was created with BioRender.com under agreement number "MS25KT3KDE".

as indicated by the *PubMed Identifier* (PMID) references. The final step was reviewing the articles obtained, then analyse them to get the appropriate results, by assessing the toxicity of the specific gene variants of each drug to the risk of SJS/TEN. This multifaceted approach ensured a thorough understanding of the complex interactions between drugs, genes and the development of SJS.

Results

The response-associated genes in drug use that induce SJS/TEN are discussed in the Tables 1-4 and the degree of evidence of pharmacogenomics correlations is provided by the *PharmGKB* annotation grading approach. According to analysis, there were seven pharmacological drugs that have potential risks to induce SJS/TEN, including allopurinol, antiepileptics (carbamazepine, lamotrigine, oxcarbazepine, phenytoin), methazolamide and nevirapine.[25, 26]

Allopurinol

Allopurinol is a uric acid-lowering drug commonly used for treating hyperuricemia and gout arthritis, with its mechanism of action on xanthine oxidase inhibition. Severe adverse drug skin reactions (SCARs) of allopurinol include SJS and TEN.[27] Pharmacogenetic studies related to the risk of SJS/TEN response to allopurinol can be seen in Table 1.

Table 1: Genetic polymorphisms associated with allopurinol responses in patients with Stevens-Johnson syndrome (SJS)

Gene	SNP	Response	*PharmGKB* LOE	Population	p-value	*PMID*
HLA-B	*HLA-B*58:01*	↑	1A	American, Oceanian, Asian, European	< 0.001	28857441
HLA-C	*HLA-C*03:02*	↑	2B	Asian, European	< 0.001	21545408
HLA-A	*HLA-A*33:03*	↑	2B	Asian, European	< 0.001	21545408

HLA: human leukocyte antigen; SNP: single nucleotide polymorphism; LOE: level of evidence; PMID: PubMed Identifier;

Antiepileptic drugs

Antiepileptic drugs (AEDs) are used to control seizures and enable patients to return to their regular lives by lowering seizure activity. AED-induced SJS and TEN are significantly more likely to occur in those with the *HLA-B*15:02* genotype.[28] AEDs such as carbamazepine, phenytoin, oxcarbazepine and lamotrigine are linked to a higher incidence of SJS/TEN. The most often given AED for adults is phenytoin. One of the most frequent causes of skin adverse effects linked to antiepileptic medications is phenytoin, which can result in TEN and SJS.[29] Lamotrigine is an aromatic AED produced from phenyltriazine that is used to treat bipolar disorder and epilepsy. It is among the class of aromatic AEDs, which collectively account for the majority of cases of SJS/TEN reactions. Lamotrigine shares a high rate of cross-reactivity with aromatic AED skin responses and its molecular structure is comparable to that of carbamazepine.[30] With a similar structure, oxcarbazepine is a keto-analogue of carbamazepine and has many of the same side effects and therapeutic indications. Because oxcarbazepine and carbamazepine have the same chemical makeup, oxcarbazepine increases the likelihood of SJS/TEN skin responses.[29] Pharmacogenetic studies related to the risk of SJS/TEN response to AEDs can be seen in Table 2.

Table 2: Genetic polymorphisms associated with antiepileptic drugs responses in patients with Stevens-Johnson syndrome (SJS)

Gene	SNP	Response	*PharmGKB* LOE	Drug	Population	p-value	*PMID*
HLA-B	*HLA-B*15:02*	↑	1A	Phenytoin	East Asian, American, Europa, Oceanian, African	0.047	25647819
HLA-B	*HLA-B*15:02*	↑	1A	Lamotrigine	East Asian, American, Europa, Oceanian, African	0.005	29238301
HLA-B	*HLA-B*15:02*	↑	1A	Oxcarbazepine	East Asian, American, Europa, Oceanian, African	0.043	24496695

HLA: human leukocyte antigen; SNP: single nucleotide polymorphism; LOE: level of evidence; PMID: PubMed Identifier;

Carbamazepine

An anticonvulsant medication called carbamazepine (CBZ) is frequently used to treat trigeminal neuralgia, bipolar disorder, epilepsy and chronic pain. Since each person has a different sensitivity to toxicity, researchers have found possible pharmacogenetic variables that could predict an individual's sensitivity to toxic epidermal necrolysis carbamazepine toxicity or HLA B 59 01, a marker for SJS.[31] Pharmacogenetic studies related to the risk of SJS/TEN response to carbamazepine can be seen in Table 3.

Table 3: Genetic polymorphisms associated with carbamazepine responses in patients with Stevens-Johnson syndrome (SJS)

Gene	SNP	Response	*PharmGKB* LOE	Population	p-value	*PMID*
HLA-B	*HLA-B*40:01*	↓	2A	East Asian	0.004	23692434
HLA-A	*HLA-A*31:01*	↓	1A	East Asian, American, Europa, Oceanian, African	0.030	21917426

HLA: human leukocyte antigen; SNP: single nucleotide polymorphism; LOE: level of evidence; PMID: PubMed Identifier;

Methazolamide

A sulfonamide derivative called methazolamide lowers intraocular pressure in glaucoma and other eye conditions by functioning as an inhibitor of carbonic anhydrase. Sulfonamides carry a significant risk of causing TEN and SJS.[32] Pharmacogenetic studies related to the risk of SJS/TEN response to methazolamide can be seen in Table 4.

Table 4: Genetic polymorphisms associated with methazolamide response in patients with Stevens-Johnson syndrome (SJS)

Gene	SNP	Response	*PharmGKB* LOE	Drug	Population	p-value	*PMID*
HLA-C	*HLA-C*01:02*	↓	2B	Methazolamide	East Asian	0.002	25918017
HLA-B	*HLA-B*59:01*	↑	2A	Methazolamide	East Asian	2×10^{-12}	25918017

HLA: human leukocyte antigen; SNP: single nucleotide polymorphism; LOE: level of evidence; PMID: PubMed Identifier;

Nevirapine

A powerful nonnucleoside reverse transcriptase inhibitor, nevirapine has been used extensively in the treatment of HIV. Nevirapine-induced hypersensitivity reactions (HSRs) result in hypersensitivity syndromes (HSS), which include SJS and TEN, which are clinically apparent.[32] Pharmacogenetic studies related to the risk of SJS/TEN response to nevirapine can be seen in Table 5.

Table 5: Genetic polymorphisms associated with nevirapine response in patients with Stevens-Johnson syndrome (SJS)

Gene	SNP	Response	*PharmGKB* LOE	Drug	Population	p-value	*PMID*
CYP2B6	*rs28399499*	↑	2A	Nevirapine	Sub-Saharan African	0.0005	4228781
HLA-C	*HLA-C*04:01*	↑	2B	Nevirapine	Sub-Saharan African	< 0.0001	3616517

HLA: human leukocyte antigen; SNP: single nucleotide polymorphism; LOE: level of evidence; PMID: PubMed Identifier;

Discussions

Significantly severe SCARs are caused by allopurinol in HLA genotypes. Similar to how HLA molecules bind covalently to larger protein structures in drug reactions (hapten carrier model), this causes an immune response that appears to be specific to certain HLA molecules. Nine *HLA-B*5801* allele populations found in the controlled investigation were substantially associated with a higher risk of allopurinol-induced SJS/TEN in the European and Japanese populations ($p < 0.001$). They were still only 50–60 % sensitive (56 % combined sensitivity).[33] Furthermore, allopurinol drug-induced SJS/TEN was substantially correlated with HLA genotypes (*HLA-C*03:02* and *HLA-A*33:03*; $p = 0.00105$ and $p = 0.0011$, respectively), particularly in individuals who were Caucasian.[34]

Among the Han Chinese population in Taiwan, the presence of *HLA-B*15:02* exhibited on association with the phenytoin-induced SJS/TEN ($p = 0.047$), lamotrigine-induced SJS/TEN ($p = 0.1266$) and oxcarbazepine-induced SJS/TEN ($p = 0.043$). The importance of the *HLA-B*15:02* allele as a risk factor for lamotrigine-induced SJS/TEN ($p = 0.005$) was further highlighted by a Thai investigation. Notably, SJS/TEN risk factors include drug-metabolising enzymes like asuridine-diphosphate-glucuronosyl-transferases (UGT) including UGT1A4 and UGT2B7, particularly with regard to lamotrigine metabolism.

The probability of developing SJS/TEN was decreased in carriers of the *HLA-B*40:01* allele ($p = 0.004$) compared to non-carriers. In a case-control design, 26 patients and 135 controls were examined in this study; cases receiving carbamazepine had progressed to SJS/TEN. Furthermore, compared to 10.3 % of healthy controls, 42.9 % of patients with carbamazepine-induced SJS had the *HLA-A31:01* allele. When comparing allele frequencies between patients with SJS and carbamazepine-tolerant controls (frequency = 14 %), no significant differences were seen. In this investigation, the strongest correlation between *HLA-A*31:01* and carbamazepine-induced hypersensitivity syndrome (CBZ-HSS) and carbamazepine-severe cutaneous adverse reactions (CBZ-SCAR) was seen.

The *HLA-B*59:01* allele ($p = 2 \times 10^{-12}$) was linked to methazolamide-induced SJS/TEN in Japanese and Korean populations. Despite showing a reduced link with *HLA-B*59:01*, *HLA-C*01:02* was still associated with a higher risk of methazolamide-induced SJS/TEN ($p = 0.002$).[13] In HIV-positive African adults, the CYP2B6 polymorphism c.983T.C (rs28399499) was found to be a risk factor for nevirapine-induced SJS/TEN ($p = 0.0005$). This polymorphism indicates enzymatic inactivity. Furthermore, in HIV cohort research conducted in Malawi, Daniel et al discovered *HLA-C*04:01* as a risk factor for nevirapine-induced SJS/TEN.[25] In conclusion, the use of a bioinformatic-based approach from *PharmGKB* is quite accurate as a comprehensive source of known genetic variations in drug response in increasing the risk of SJS/TEN. In this article, the drug data is obtained

from the level of evidence with criteria level 1A to 2B. Future research is anticipated to include additional levels (from 1A to 4). The level of drug assessment taken in this article is still limited, necessitating the increase the variety of drugs for further in-depth studies.

Conclusion

In summary, this study highlighted key gene variants, notably *HLA-A, HLA-B, HLA-C* and *CYP2B6*, associated with an increased susceptibility to the SJS and TEN. These findings emphasise the potential of genetic screening as a proactive tool to identify individuals at risk of adverse reactions to specific medications. By leveraging this systematically-based genetic insight, healthcare practitioners are able tailoring treatment strategies and mitigating the likelihood of SJS induced by medications, including allopurinol, phenytoin, lamotrigine, oxcarbazepine, methazolamide, carbamazepine and nevirapine. Screening for these gene variants holds promise, particularly in populations with these risk alleles. Identifying vulnerable individuals enables healthcare providers to optimise therapeutic decisions and minimise the SJS and TEN incidences associated with the studied medications. This personalised approach enhances treatment safety and exemplifies the shift towards precision medicine, aligning interventions with an individual's genetic profile. There were limitations in taking evidence based on level 1A to 2B criteria only, which limited the drugs and gene variants discussed. Further research is needed to include further evidence based on the six levels from 1A to 4, as well as genetic information to be harmonised across countries/regions to improve the application of pharmacogenomics in the future.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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