Genetics of Severe Cutaneous Adverse Reactions

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Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug rash with eosinophilia and systemic symptoms (DRESS) are T cells-mediated life-threatening immune reactions, most commonly induced by drug. The last decade has seen significant progress in SCARs research. Recent studies have unveiled the pathogenesis of SCARs involved in susceptible genes, including human leukocyte antigens (HLA) and drugs-T cell receptor (TCR) interaction that may trigger T cell activation with downstream immune signaling of cytokines/chemokines and specific cytotoxic proteins releases. Advances in identification of multiple genetic alleles associated with specific drugs related SCARS in different populations is an important breakthrough in recent years for prevention of SCARS. This article summarized the findings on genetic factors related to SJS/TEN, especially for HLA.

Keywords: genetic screen, Stevens–Johnson syndrome, toxic epidermal necrolysis, pharmacogenomic, severe cutaneous adverse drug reactions

INTRODUCTION

Cutaneous reactions are most common manifestations seen in hypersensitivity reactions of drugs, named cutaneous adverse drug reactions, and among those with risk of life-threatening are classified into severe cutaneous adverse reactions (SCARs), mediated by drug-specific T lymphocytes, including drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN). The mortality rates for SJS/TEN are ~5–10% in SJS and 30–50% in TEN (1), and the common leading culprit drugs around the world are antibiotics, antiepileptics, allopurinol, and cold medicine (2–4). In this article, we reviewed the updated molecular mechanism and susceptible genes related to SCARs.

Immune Mechanisms and Clinical Manifestations of Severe Cutaneous Adverse Reactions

SCARs belonged to type IV hypersensitivity reaction and are T cell-mediated immune responses with different effector cells and cytokines, resulting in further subtypes with specific clinical features.
SJS/TEN is characteristic for cutaneous and mucosal detachment, commonly including oral, ocular, and genital or anal mucosae. Internal epithelial organs are rarely involved, concerning mainly in the respiratory and gastrointestinal tract (5). SJS/TEN is one of the representative SCARs with high mortality and complications, where CD8+ cytotoxic T lymphocytes (CTLs) play a role, acting as effector cells with nature killer cells, causing cell death by the participant of perforin/granzyme B, granulysin, and/or Fas-Fas ligand (6). Besides, cytokines/chemokines, including interleukin (IL)-6, IL-8, IL-15, C-C chemokine receptor 10, tumor necrosis factor-α, interferon-γ, etc., also contribute to these severe immune reactions (7). The messenger RNA expression and level of 15-kDa granulysin were found much higher than others in SJS/TEN blister cells, suggesting it is the key mediator of disseminated keratinocyte apoptosis (8).

Another severe phenotypes of SCARs is DRESS, presenting as long-lasting, widespread, and infiltrated skin rash with internal organ involvement and hematological abnormalities, most frequently as eosinophilia and atypical lymphocytes (9). The immune mechanism involved in DRESS is majorly the Th2 immune response. Th2 cells involved in DRESS secrete ILs, including IL-5, IL-4, and IL-13, promoting immunoglobulin E and immunoglobulin G4 production and macrophage deactivation, leading to mast cell and eosinophil activation (6). Perforin/granzyme B, tumor necrosis factor-α, interferon-γ, C-C chemokine receptor 4, and thymus and activation-regulated chemokine (10) are also engaged.

Molecular Mechanism and Susceptible Genes Related to Severe Cutaneous Adverse Reactions

Roujeau et al. firstly reported the relationship between human leukocyte antigen (HLA) and SJS in 1986 (11) and HLA and TEN in 1987 (12). The association of HLA and SCARs are drug-specific and ethnicity-specific (13). Specific HLA is not only a genetic marker but also plays an important role in the pathogenesis of SCARs by presenting drug antigen to T cell receptor (TCR) and causing T cell-dependent immune response (14).

Recent advance in the technology of pharmacogenomic studies have showed more genetic risk factors associated with SCARs, not only in genes of HLA and other immune pathways, but also in drug metabolism or elimination. The genetic approach for the pharmacogenomics studies for SCAR has been evolved from sequencing based genotyping with polymerase chain reaction (PCR), such as HLA genotypes (15) to more comprehensive approaches, including genome-wide association study (GWAS) and next-generation sequencing (NGS), in discovering the relationship between adverse drug reactions (ADRs) and genotyping, and discovered more non-HLA loci (15–17).

Genetic Susceptibility to Aromatic Antiepileptic Drug-Induced Severe Cutaneous Adverse Reactions

Aromatic antiepileptic drugs (AEDs) are commonly used mainly in treating epilepsy and neuralgia, including carbamazepine (CBZ), oxcarbazepine (OXC), lamotrigine (LTG), phenytoin (PHT), and phenobarbital (PB). A strong association of HLA-B*15:02 with CBZ-induced SJS/TEN was first found in Han Chinese (18). This relationship was also proved in Southeast Asians, including Thais (19), Malaysians (20), Indians (21).

AEDs had the same chemical structure, an aromatic ring, thus sharing the same risk allele. The susceptibility of HLA-B*15:02 with AED-induced SJS/TEN was also found in PHT (22) and OXC (23), causing SJS/TEN in Han Chinese and Southeast Asians (24–26) (Table 1).

By using GWAS approach, our previous study found that CYP2C9*3 was significantly related to PHT-induced SCARs in Han Chinese, Japanese and Malaysian, and by adding HLA-B*15:02 to this variant could increase sensitivity for preemptive test (35). In addition to HLA-B*15:02, HLA-B*13:01, and HLA-B*51:01 were also found strong association with PHT-induced SCARs in Han Chinese, Thai and Japanese (37). Another genetic variant for PHT-induced SCARs was HLA-B*15:13, which majorly found in Malaysian (24) (Table 1).

The HLA-DRB1*15:01 allele had been reported to be associated with AED-induced SJS/TEN in Han Chinese (68). Besides, HLA-A*33:03, HLA-B*58:01, HLA-B*40:01, and HLA-DRB1*03:01 alleles had also been reported to be associated with AED-induced SJS/TEN (68, 69).

There were differences of susceptible genes among ethnic groups. The same susceptible genotype of HLA-B*15:02 of CBZ-induced SJS/TEN was not found in Northeast Asians like Japanese and Korean, but HLA-B*15:11 instead (27, 28, 63). Interestingly, association between HLA-B*15:21 and CBZ-induced SJS was found in an HLA-B*15:02 negative Thai patient (29). The relationship of HLA-B*15:11 and HLA-B*15:21, member of HLA-B75 serotype, and CBZ-induced SJS/TEN was found in HLA-B*15:02 negative patients with pooled-data of Southeast Asian (29) (Table 1).

As for other AEDs in Northeast Asians, HLA-B*51:01 was found to be related to PHT- and PB-induced SJS/TEN, and HLA-A*02:07 was found to be relevant with PB- and zonisamide-induced SJS/TEN (36) (Table 1).

Caucasians also revealed less relevant of AEDs and HLA-B*15:02, instead, they were commonly found with HLA-A*31:01, and developed CBZ-induced DRESS (31, 32). This relationship also existed in Han Chinese and Japanese (31, 70), however, not only DRESS but also SJS/TEN were related with this gene in Japanese (70). Another Caucasian-specific gene was HLA-B*57:01 and was found to be strongly associated with CBZ-induced SJS/TEN in Europeans (30). A limited number also showed a relationship with HLA-B*38 and LTG-induced SJS/TEN (34) (Table 1).
| Causative drug       | Genetic associations | SCAR   | Ethnicity        | Reference | Clinical implementations and recommendations |
|---------------------|----------------------|--------|------------------|-----------|-----------------------------------------------|
| **Antiepileptic drug** |                      |        |                  |           |                                               |
| Carbamazepine       | B’15:02              | SJS/TEN| Han Chinese      | (18, 25) | 1. Labeled by Taiwan FDA, Hong Kong Department of Health, Singapore Ministry of Health, Thailand HITAP, India MOHFW, US FDA, Canada HCSC, EMA. 2. National health insurance subsidized in Taiwan, China, Hong Kong, Singapore, and Thailand. |
|                     | B’15:11              | SJS/TEN| Southeast Asian  | (19, 20) |                                               |
|                     | B’15:21              | SJS/TEN| Southeast Asian  | (29)      |                                               |
|                     | B’57:01              | SJS/TEN| Caucasians       | (30)      |                                               |
|                     | A’31:01              | DRESS  | Han Chinese      | (31)      | 1. Labeled by US FDA, Canada HCSC, Japan, and Taiwan. |
|                     |                      |        | Caucasians       | (31, 32) |                                               |
|                     |                      |        | Japanese         | (33)      |                                               |
| Oxcarbazepine       | B’15:02              | SJS/TEN| Han Chinese      | (23, 25) | 1. Labeled by US FDA, EMA and Taiwan FDA. 2. Ongoing clinical trial in Taiwan and China. |
| Lamotrigine         | B’15:02              | SJS/GEN| Han Chinese      | (25)      | Ongoing clinical trial in Taiwan and China.   |
|                     | B’38                 | SJS/TEN| Caucasians       | (34)      |                                               |
| Phenytoin           | B’15:02              | SCARs  | Han Chinese      | (22, 25, 35) | 1. Labeled by Canada HCSC, US FDA, and Taiwan FDA. 2. Ongoing clinical trial in Taiwan and China. |
|                     | B’13:01              | SCARs  | Asian            | (35)      | Ongoing clinical trial in Taiwan and China.   |
|                     | B’15:13              | SJS/TEN| Japanese         | (36)      | Ongoing clinical trial in Taiwan and China.   |
|                     | B’51:01              | SCARs  | Han Chinese      | (37)      |                                               |
|                     | CYP2C9*3             | SCARs  | Asian            | (35)      | Ongoing clinical trial in Taiwan and China.   |
| Phenobarbital       | B’51:01              | SJS/TEN| Japanese         | (36)      |                                               |
|                     | A’02:07              | SJS/TEN| Japanese         | (36)      |                                               |
| Zonisamide          | A’02:07              | SJS/TEN| Japanese         | (36)      |                                               |
| **Antiinfection drugs** |                      |        |                  |           |                                               |
| **Antibiotics**     |                      |        |                  |           |                                               |
| Co-trimoxazole      | B’13:01              | SCARs  | Han Chinese      | (17)      |                                               |
|                     |                      |        | Southeast Asian  |           |                                               |
| Piperacillin/tazobactam | B’62                | DRESS  | Caucasians       | (38)      |                                               |
| Sulfamethoxazole    | B’38                 | SJS/TEN| Caucasians       | (34)      |                                               |
| Vancomycin          | A’32:01              | DRESS  | Caucasians       | (39)      |                                               |
| **Anti-virus**      |                      |        |                  |           |                                               |
| Abacavir            | B’57:01              | HSR    | Caucasians       | (40, 41) | Labeled by US FDA, US HHS, EMA, Canada HCSC, and multiple international HIV/AIDS organizations |
|                     |                      |        | Hispanic         | (42)      |                                               |
|                     |                      |        | Indian           | (43)      |                                               |
| Nevirapine          | B’35:05              | HSR    | Thai             | (44)      |                                               |
|                     | C’04:01              | SJS/TEN| African          | (45)      |                                               |
|                     | Ow’04                | cADRs  | All              | (46)      |                                               |
|                     | Ow’08                | HSR    | Sardinian        | (47)      |                                               |
|                     |                     |        | Japanese         | (49)      |                                               |
|                     | DRB1’01:01           | HSR    | Caucasians       | (49)      |                                               |
|                     | CYP2B6               | cADRs  | All              | (46)      |                                               |
|                     | CCHCR1               | HSR    | Thai             | (44)      |                                               |
| Raltegravir         | B’53:01              | DRESS  | African          | (50)      |                                               |
| **Anti-leprosy**    |                      |        |                  |           |                                               |
| Dapsone             | B’13:01              | DHS    | Han Chinese      | (51)      | Prospective screening in China.               |
|                     |                      |        | Korean           | (52)      |                                               |
|                     |                      |        | Indonesian       | (53)      |                                               |
|                     |                      |        | SCARs            | (54)      |                                               |

(Continued)
TABLE 1 | Continued

| Causative drug | HLA allele | SCAR | Ethnicity | Reference | Clinical implementations and recommendations |
|----------------|------------|------|-----------|-----------|------------------------------------------------|
| **Cold medicine** |            |      |           |           |                                                 |
|                | A*02:06    | SJS/TEN | Japanese  | (65)      |                                                 |
|                |            |       | Korean    | (55, 57)  |                                                 |
|                | A*66:01    | SJS/TEN | Japanese  | (55)      |                                                 |
|                | B*44:03    | SJS/TEN | Indian    | (56)      |                                                 |
|                |            |       | Thai      | (59)      |                                                 |
|                |            |       | Brazilian | (56, 58)  |                                                 |
|                | C*03:04    | SJS/TEN | Korean    | (57)      |                                                 |
|                | C*12:03    | SJS/TEN | Brazilian | (58)      |                                                 |
|                | TLR3        | SJS/TEN | Japanese  | (60)      |                                                 |
|                | PTGER3      | SJS/TEN | Japanese  | (63)      |                                                 |
|                | IKZF1       | SJS/TEN | Japanese  | (61)      |                                                 |
| **Others**     |            |      |           |           |                                                 |
| Allopurinol    | B*58:01    | SJS/TEN | Thai       | (62)      | 1. Recommendation in the American College        |
|                |            |       |           |           | of Rheumatology guidelines for allopurinol      |
|                |            |       |           |           | initiation in Asians.                           |
|                |            |       |           |           | 2. National health insurance subsidized in        |
|                |            |       |           |           | Taiwan, China, Korea, and Thailand.             |
| Methazolamide  | B*59:01    | SJS/TEN | Northeast Asian | (66) | |
|                |            |       | Han Chinese | (67) | |

DHS, Dapsone hypersensitivity syndrome; HSR, hypersensitivity reaction.

Genetic Susceptibility to Antibiotics Induced Severe Cutaneous Adverse Reactions

Antibiotics are one of the most widely used medications, being responsible for one-fifth to one-third of ADRs (71, 72). The most common cause of SCARs induced by antibiotics are beta-lactams; others include sulphonamide antibiotics, fluoroquinolones, macrolides, tetracyclines, and glycopeptides (71). Above all, vancomycin is notable for causing DRESS. The relevant susceptible gene found with vancomycin-causing DRESS was HLA-A*32:01, with a strong association in Caucasians (39). Other possible genes as a risk factor in Caucasian were HLA-B*38 with sulfamethoxazole-induced SJS/TEN (34) and HLA-B*62 with piperacillin/tazobactam-induced DRESS (38), yet further research is still needed due to number limitation (Table 1).

Antibiotics, AEDs, and allopurinol are the most common offending drugs causing SJS/TEN in China from our previous study (4). Although the finding of genetic susceptibility with antibiotic-induced SCARs was limited, our recent study by using whole genome sequencing (WGS) approach showed HLA-B*13:01, not metabolism enzymes, was strong associated with co-trimoxazole-induced SCARs in Asians, including Han Chinese, Thai, and Malaysian (17) (Table 1).

Dapsone is mainly used in the treatment of leprosy and can also apply in other dermatological inflammatory diseases due to the ability of anti-infection and anti-inflammation. Dapsone hypersensitivity syndrome is the potentially fatal adverse effect of dapsone, presenting as fever, skin rash, lymphadenopathy, and multiple systemic involvements. By using GWAS approach, the susceptible gene of DHS was first found in Han Chinese with HLA-B*13:01 (51), which mainly exists in Asians. The same result was validated in Koreans (52) and Indonesians (53). This gene was also susceptible in Thai with dapsone-induced SCARs (54), including DRESS and SJS/TEN (Table 1).

Genetic Susceptibility to Antivirus Induced Hypersensitivity Reactions

Abacavir is a nucleoside reverse transcriptase inhibitor and is used as one of the combination treatment of human immunodeficiency virus (HIV) infection. Hypersensitivity reactions induced by abacavir appear in ~5–8% of Caucasians (73), which presented as fever, rash, gastrointestinal tract, and respiratory symptoms during the first 6 weeks of initiation. These symptoms are non-specific; however, being a delayed-type immune reaction, a patch test can easily help to distinguish hypersensitivity reactions (73). The relevant susceptible gene HLA-B*57:01 was found in white and black population (40, 41), especially white (74), and also Hispanic (42) and Indian children (43). A study in Hong Kong found a 0.5% positive rate with HLA-B*57:01 in HIV-positive patients of Han Chinese, thus suggesting that screening in this population is unnecessary (75) (Table 1).

Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI), and is also a medication treating HIV infection.
The association of susceptible gene was first found with HLA-DRB1*01:01 in nevirapine-induced HSR in Western Australian (49). However, this gene was later proven more associated with hepatotoxicity rather than cADRs in Caucasian (46). Other susceptible gene found in nevirapine-induced hepatotoxicity were HLA-Cw*08 in Japanese (29), HLA-Cw*04 in Han Chinese (76), and HLA-DQB1*05 in Caucasian (46). Both HLA-Cw*08 and HLA-Cw*04 were found relevant to nevirapine-induced HSR and hepatotoxicity. Relationships between HLA-Cw*08 and HSR were found in Sardinian (47) and Japanese (29). HLA-Cw*04 was found commonly in nevirapine-induced cADRs in Han Chinese, Thai, Spain, African and Caucasian, especially African and Asian (46). CYP2B6 was also participated due to affecting delayed plasma clearance of nevirapine (46). Besides, HLA-B*35:05 was found to be predictable with nevirapine-induced skin rash in Thai (44), whereas the same relationship was found weak in Han Chinese and Caucasian (46). In addition to HSR, SJS/TEN was found in patients using nevirapine, associated with HLA-C*04:01 in African (45), and recently, the association between genetic variations in CCHCR1 and nevirapine-induced HSR was also found in Thai (77). GWAS approach was used in both studies (Table 1).

Raltegravir is an integrase inhibitor that is also used in the treatment of HIV infection, and HLA-B*53:01 was found strongly associated with raltegravir-induced DRESS in Africans (50) (Table 1).

Genetic Susceptibility to Cold Medicine Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

The term cold medicine comprises non-steroidal anti-inflammatory drugs and other multi-ingredient medications. Due to the high prevalence of cold and the use of cold medicine, SJS/TEN developed after patients using cold medicines is not uncommon, and a series of susceptible genes had been reported to be related to cold medicine-induced SJS/TEN, especially with severe ocular complications. The association of HLA-A*02:06 and HLA-B*44:03 was found to be associated with cold medicine-induced SJS/TEN in Japanese (55), and the same susceptible genes were verified in patients of other populations, such as HLA-B*44:03 in Indian and Brazilian, and HLA-A*02:06 in Korean (56). Besides, HLA-C*03:04 was also reported to be associated with cold medicine-induced SJS/TEN in Korean (57). Furthermore, HLA-A*66:01 and HLA-C*12:03 was found related in Brazilian (58) and HLA-B*44:03 and HLA-C*07:01 found in Thai (59). In summary, HLA-B*44:03 seems to be a cross-ethnic susceptible gene with a strong association in Japanese, Brazilian, Indian, and Thai, whereas HLA-A*02:06, HLA-B*44:03, toll-like receptor 3 (TLR3), prostaglandin-E receptor 3 (PTGER3), and IKZF1, by using GWAS approach, were identified as primary association to cold medicine-induced SJS/TEN with severe ocular involvement in Japanese (55, 60, 61, 78) (Table 1).

Genetic Susceptibility to Allopurinol-Induced Severe Cutaneous Adverse Reactions

By inhibiting xanthine oxidase and then reducing the synthesis of uric acid, allopurinol is a first-line drug used to treat hyperuricemia and gout and also remains to be one of the leading causes of SCARs. HLA-B*5801 was first found as an important genet marker of allopurinol-induced SCARs in Han Chinese (64). The same associations were validated in Thai (62), Japanese (63), Korean (65), and Caucasians (34). However, the pharmacogenomic associations varied from different ethnic populations, 50–60% in Caucasians and Japanese, and 80–100% in Korea, Thai, and Han Chinese (79). Other non-genetic factors may also contribute to allopurinol-induced SCARs, especially impaired renal function, cardiovascular diseases, and higher drug initiating dosages (80) (Table 1).

Genetic Susceptibility to Methazolamide-Induced Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

Carbonic anhydrase inhibitor methazolamide is a medication applied in lowering intraocular pressure, for example, as a patient with glaucoma. Despite the low frequency, methazolamide may potentially induce SJS/TEN. Strong association of HLA-B*59:01 and methazolamide-induced SJS/TEN in Korean and Japanese had been reported (66) and also in Han Chinese (67) (Table 1).

Jackpot Theory and Importance of Specific T Cell Receptor for the Development of Severe Cutaneous Adverse Reactions

Although previous studies proved the association of specific HLA genotypes with SCARs, the positive predictive values were mostly low (81). Our previous study showed CBZ-specific T cells expressing specific TCR from peripheral blood mononuclear cells and causing activation of granulysin release in HLA-B*15:02-positive CBZ-induced SJS/TEN but was not found in CBZ-tolerant individuals or other drug-related SJS/TEN (82). Similarly, preferential usage of TCRβ variable gene and clonal expansion of specific third complementarity-determining region (CDR3) was identified in blister cells of patients with allopurinol-induced SJS/TEN (83). More recently, our further study showed a public αβTCR was further identified from CTLs of patients with CBZ-induced SJS/TEN, with a paired TCRβ CDR3 clonotype “ASSLAGELF” and TCRα CDR3 clonotype “VFDMNTDKLI,” which react to CBZ and its structural analogs by its structural analogs and bind affinity and mediate immune response (84). Importantly, the specific CDR3 clonotype was present in CTLs of CBZ-induced SJS/TEN of patients from different populations (Chinese or Europeans) with or without the HLA-B*1502 genotype. The finding of clonotype-specific T cell and drug-specific public TCR in patients illustrated the essential molecular role of shared and restricted TCR that interacted with specific HLA and drugs for the development of SCARs (Jackpot theory).
Pharmacogenomic Test for Prevention of Severe Cutaneous Adverse Reactions

The burden of developing SCARs was life-threatening. Not only public health but also medical resources were affected. A team in Singapore observed higher laboratory costs in the residency of patients with ADRs (85).

Considering the mortality rate and economic burden of SCARs, an easy and effective method for the prevention of SCARs would be greatly needed. The development of a strong correlation of preemptive genetic tests for high-risk medications related to SCARs is therefore very helpful. By screening relevant genes before using susceptible culprit drugs, we should be able to prevent the occurrence of SCARs and the consequent cost for sequelae.

Genetic testing of HLA-B*15:02 before CBZ was warned by The Food and Drug Administration (FDA) of the United States, Taiwan, and similar agencies of other countries (86), and genetic testing of HLA-B*58:01 before allopurinol initiation was warned by the FDA of Taiwan or other Asian countries (Table 1). Recommendations of relative gene testing before culprit drugs in case of developing SCARs were noticed in various studies (87). The first prospective screening test was applied in patients with HIV infection needed for abacavir and demonstrated a significantly lower incidence in the HLA-B*57:01 screening group (74). For proof of concept and clinical implementation, the Taiwan SJS Consortium had conducted a clinical trial to prevent CBZ-induced SCARs by genotyping DNA with HLA-B*15:02 allele of 4,877 candidates before CBZ therapy and found no SJS/TEN with negative subjects (88). The other one of the most commonly used drugs and cause of SCARs in Taiwan was allopurinol. Prospective screening with HLA-B*58:01 enrolled 2,926 patients before initiation of allopurinol in Taiwan, and the result showed none of the negative subjects developed SCAR (89). Recently, a prospective study of 1,539 patients diagnosed with leprosy underwent HLA-B*13:01 genotyping before using dapsone in China, and the result showed no SCARs developed in non-carrier (90) (Table 1).

Implementation of Precision-Based Use of Antiepileptic Drug Therapy by Screening Multiple Risk Alleles Related to Aromatic Antiepileptic Drugs for Prevention of Severe Cutaneous Adverse Reactions

With a similar aromatic ring structure, the first line AEDs, such as CBZ, OXC, LTG, PHT, and PB, have potential and share similar risk alleles predisposing to SCARs. For consideration of efficacy and safety for clinical selection of AEDs, a piece of pharmacogenomics information is important for decision making for patients with epileptic or neurologic disorders. Therefore, pharmacogenomic panel testing for multiple risk alleles related to all AEDs has its clinical necessity and demand; for clinical implementation and to evaluate the feasibility and efficacy of a pharmacogenomic panel of AEDs, we have developed a rapid testing panel of multiple risk alleles, including HLA-B*15:02, CYP2C9*3, HLA-B*13:01, HLA-B*51:01, and HLA-A*31:01, which are strongly related to aromatic AED-induced SCARs (Table 2) for decision making before initiating AEDs. A clinical trial has started since 2018 in Taiwan and China of multiple medical centers, by enrolling patients with need of antiepileptic drugs without history of using, and performing the testing panel by quantitative polymerase chain reaction (qPCR). With avoiding relevant drugs with positive susceptible genes, a preliminary evaluation of 231 patients with negative corresponding risk alleles received aromatic AEDs therapy, no SCARs have been observed, although five patients developed milder maculopapular eruption or itchy skin lesions.

CONCLUSIONS

SCARs are rare but life-threatening. The findings of the relationship with susceptible genes and drugs lead to clinical applications of prevention. By screening the known relevant genes before prescribing potentially culprit drugs in corresponding ethnicities would be an effective method to avoid the development of SCARs.

AUTHOR CONTRIBUTIONS

S-CY, M-YL, Z-YZ, X-YJ, MH, Y-FZ, C-BC, and W-HC wrote the original draft. X-YJ, MH, and Y-FZ provided the resources. S-CY, M-YL, Z-YZ, C-BC, and W-HC reviewed and edited the draft. C-BC and W-HC conceptualized the review and acquired funding. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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