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REVIEW

# HLA-associated adverse drug reactions - scoping review

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**Abstract**

Alleles of the human leukocyte antigen (HLA) system have been associated with the occurrence of idiosyncratic adverse drug reactions (ADRs). Accordingly, it is assumed that pre-emptive testing for the presence of certain HLA alleles (HLA-typing) could prevent these ADRs in carriers. In order to perceive the current evidence for HLA-associated ADRs, we conducted a scoping review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The literature search on PubMed and on Embase was carried out on the July 8 and 9, 2020, respectively. To be included in the scoping review, the studies had to investigate an association of any HLA-associated ADR with any small molecule approved and available on the Swiss market. We considered English and German primary literature published since 2002. A total of 149 studies were included, whereof most were retrospective, whereas one was a prospective randomized controlled trial. The majority of the studies ($n = 33$) described the association of HLA-B*15:02 with carbamazepine. It was not possible to directly compare the studies, as they were too heterogeneous in terms of the ADR definition, the HLA alleles, the number of participants, and the study types. Therefore, we summarized the results in a descriptive manner. Even if an interpretation of the outcomes remains open, the descriptive overview revealed the prevailing complexity and uncertainty in the field. For the future, consistent definitions on the different phenotypes need to be established and applied and the reporting of association studies should follow a harmonized structure.

## INTRODUCTION

Adverse drug reactions (ADRs) are a major concern in health care. Besides the substantial economic burden, they can lead to hospitalization[1] or even death of patients. Stevens-Johnson syndrome (SJS) and the toxic epidermal necrolysis (TEN) are both examples of life-threatening ADRs presenting as delayed hypersensitivities, which are often associated with different variants of the human leukocyte antigen (HLA). HLA is part of the adaptive immune system. Presenting peptides to T-cells, the highly polymorphic HLA receptors are responsible for immune recognition as part of the immune response.[2,3] The HLA genes consist of different variant alleles, thereby leading to different binding specificities of the HLA proteins.[3] It has been shown that drugs and endogenous proteins can

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interact with certain HLA molecules, thereby leading to the formation of an immunogenic self-peptide complex. These complexes are recognized by the immune system inducing an autoimmune-like reaction[4] and are assumed to be determinants of hepatic and cutaneous ADRs known as drug-induced liver injury (DILI) and drug-induced skin injury (DISI), respectively. Liver failure due to DILI is often life-threatening,[5] and assumed to be responsible for approximately 15% of the cases of acute liver failure in Europe and the United States.[6] The incidence of DISI is approximately 5–15% of all ADRs.[7] SJS and TEN are the most severe phenotypes associated with long-term morbidity and high mortality.[8]

The use of pharmacogenetic (PGx) testing, where a genetic test is associated with a certain drug treatment, to prevent ADR is extensively discussed these days.[9–11] However, the clinical benefit of pre-emptive (prior to therapy start) PGx testing is still controversial. Although being considered one part of individualized medicine,[12,13] there are also voices saying that it is too early for implementation of PGx testing in medical routine.[14] However, it is uncontested that PGx findings contributed significantly to our current understanding of drug metabolism, drug response, and drug safety.

In a previous project,[15] we elaborated an overview on how PGx information is presented in Swiss drug labels (DLs). We identified all PGx-relevant sections, extracted the mentioned biomarkers, and anatomic groups, and classified the available PGx information according to the four PGx levels proposed by Pharmacogenomics Knowledgebase (PharmGKB).[16] Moreover, we reported on how precise the instructions on PGx testing and its consequences for drug therapy are. Within our analysis, we identified DLs where pre-emptive testing is required. One of the identified DLs was that for abacavir, where pre-emptive testing for HLA-B*57:01 is required to prevent administration to patients with a higher risk of hypersensitivity reaction.[17] This suggested practice is supported by the findings of "PREDICT-1" (a randomized controlled trial [RCT] including 1650 patients), published in 2002,[18,19] where carriers of the HLA-B*57:01 allele showed a higher risk to develop the abacavir hypersensitivity syndrome compared to non-carriers (odds ratio [OR] 117 [29–481]).[19] Especially in the case of HLA alleles (e.g., abacavir[18]), it has been suggested that so-called HLA-typing (pre-emptive testing for a specific HLA allele) may prevent the associated ADRs if exposure of carriers of certain HLA alleles is avoided.[18] Besides abacavir, there are other examples of clinically applied drugs (e.g., carbamazepine,[20] allopurinol,[21] or oxcarbazepine[22]) where ADRs are assumed to be associated with HLA alleles. Nevertheless, translation into clinical practice is still limited. Presumably, due to the opinion of various health care professionals (HCPs) saying that there is insufficient evidence for HLA-typing in association with a drug intervention. It was the aim of the herein reported project to identify and summarize studies investigating HLA alleles in relation to ADRs and to give an overview of the evidence on the described ADRs and the investigated genetic factors.

# METHODS

## Analysis of the Swiss drug labels

We have screened all 4306 Swiss DLs (also known as Summary of Product Characteristics [SmPC]) describing the 15,367 products on the Swiss market in German for PGx information by natural language processing (NLP). Here, we report the substances identified by NLP mentioning HLA alleles as biomarker and the respective phenotypes of the adverse event. For details on the systematic analysis of the Swiss DLs, please refer to ref. 15

## Literature search

For our literature search, we defined three determinants, namely HLA for the different human leucocyte antigen (HLA) alleles, ADR (phenotype) for the different adverse drug reactions (ADRs), and DRUG for the different active substances involved. The strings applied in the literature search on Pubmed and Embase are available as Supplementary File S1, and S2. The literature search was carried out on PubMed and on Embase on July 8, 2020, and on July 9, 2020, respectively. The publications were extracted into an Endnote library. We performed the scoping review according to the recommendation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23]

## Definition of phenotype

For the definition of the phenotypes, we referred to the Phenotype Standardization Project,[24] where the ADRs (drug-induced torsade de pointes, DILI, and DISI) involving HLA alleles are defined.[24] Notably, due to the various existing terminologies for cutaneous ADRs, we have to specify that DISI is a collective term including severe cutaneous manifesting phenotypes such as SJS/TEN, acute generalized exanthematous pustulosis (AGEP), and the hypersensitivity syndrome (HSS), also called drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS).[24] However, the definition of DISI by the Phenotype Standardization Project does not include the maculopapular exanthema (MPE).[24]

## Nomenclature of HLA alleles

For the nomenclature of HLA alleles, we refer to the naming rules of Marsh et al. (http://hla.alleles.org/nomenclature/naming.html).[25]

## Eligibility criteria

We included studies that investigated an association between the frequency of a certain HLA allele and the occurrence of any ADRs during the intake of a certain active substance. Inclusion was irrespective of ethnicity. However, we restricted our literature search to small molecules approved and available on the Swiss market. We considered English and German primary literature published since 2002 as in this year, the preliminary work for the first RCT with PGx testing (PREDICT-1) was conducted.[19] We included (non)-randomized controlled trials (n-RCT), case-control studies, cohort studies, and case reports. Furthermore, genomewide association studies (GWAS) examining frequencies of single nucleotide polymorphisms (SNPs) to identify alleles contributing to a specific phenotype were included.

Book chapters, conference abstracts, workshop proceedings, poster presentations, oral presentations, dissertations, and letters to the editor were excluded. In addition, we excluded articles with no access to the abstract, or if no author could be identified. During full text screening, authors of articles with no access to the full text were contacted. Finally, articles where we could not establish access to full text were excluded. See Table 1 for details on the inclusion and exclusion criteria.

**TABLE 1** Eligibility criteria for articles identified by literature search

| Inclusion |
|---|
| • Investigation of an association (positive, negative, or protective) between the frequency of an HLA allele and the occurrence of adverse drug reactions (ADRs) |
| • Human (all ethnies) |
| • Drug (small molecules) available on the Swiss market |
| • Primary literature in English or German language |
| • Publication from year 2002 onward |
| ◦ Intervention studies (randomized controlled trials [RCTs]) |
| ◦ Analytical studies (case-control studies [CCSs]), PGx analysis (PGxA), cohort studies (CSs), genomewide association studies (GWASs), and case reports (CRs)→Retrospective and prospective settings |
| **Exclusion** |
| • HLA disease related |
| • Vaccines, blood products |
| • Stem cell donation, transplantation |
| • Allergens (venom, solvents) |
| • Assay development, laboratory genotyping method |
| • Structural elucidation of HLA regions and discovery of new loci (unless association with ADRs and small molecule drug) |
| • In silico docking |
| • Secondary literature |
| • HLA in immunology (e.g., T cell-binding assay) |
| • Altered efficacy due to HLA alleles described |
| • Cost-effectiveness studies |
| • No author and/or no abstract available |
| • Study types such as conference reports, posters, letter to the editors |
| • Drug not approved for the Swiss market |

## Selection of publications

Duplicates of citations retrieved from PubMed and Embase were removed and then a title/abstract screening followed by a full text screening was carried out. Eligibility was assessed by two investigators (authors U.W. and C.J.). Any disparity was resolved by consensus. We applied the same procedure for full text screening. The screening process was documented in Endnote (Clarivate Analytics, version X9).

## Data charting process and quality assessment

The results of each study included were summarized in a descriptive manner without assessment of the quality of the respective study. Data extraction was performed by one investigator (U.W. or C.J.), whereas a second investigator (C.J. or U.W.) checked the workflow for completeness and accuracy. Disagreements were resolved by consensus. Table 2 summarizes the extracted data items. For the control populations, we differentiated between drug-tolerant controls (tolerant for the investigated drug) and other control groups (e.g., general population). If the control population was not a drug-tolerant control group, we specified it in the comment column of Table S1 Raw Data.

## Synthesis of results

For an overview, we gathered all studies in Table S2 PRISMA Scoping Review. In terms of study types, we differentiated between double-blind randomized studies, case-control studies, PGx analysis (defined as studies where selected genotypes were used to define the study groups), GWAS, cohort studies, and exploratory studies. In the table, we sorted the substances and substance groups according the Anatomic Therapeutic Chemical (ATC) code in the fifth level, which refers to the anatomic groups. From each report, we provide the biomarker identified in multiple studies, which confirmed positive associations. In addition, we reported the corresponding phenotype of the ADR, the total number, and type of studies for the substance. For analysis and discussion, we extracted the remaining identified biomarkers, where we differentiated among positive

**TABLE 2** Extracted data items

| | |
|---|---|
| **Details on reference** | Author, year, study type, drug, biomarker (HLA allele), phenotype, ethnicity |
| **Participants** | Cases (patients with ADR) with number of carriers per cases<br>controls (patients without ADR) with number of carriers per controls |
| **Further relevant data items for the search** | Odds ratio (OR), positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity, and a final rating (by the authors of the study) |

Abbreviation: ADR, adverse drug reaction.

(confirmed association), negative (no association), and protective (HLA allele demonstrated possible protective effects). Importantly, if there was no HLA allele specifically investigated in multiple studies, we listed them in the HLA alleles (or the respective single nucleotide polymorphism), or allele combinations investigated. The raw data with all the essential information collected from the studies (see data charting process) are listed in the Table S1 Raw Data.

# RESULTS

## Analysis of Swiss drug labels

At first, we conducted an analysis of the Swiss DLs in order to identify those mentioning HLA as a biomarker in the context of a therapeutic intervention. This analysis conducted by NLP revealed eight drugs mentioned in association with HLA-alleles and adverse drug events. The identified substances are summarized in Table 3.

## Selection of publications

The subsequently conducted literature search yielded 2193 articles. After removal of duplicates ($n = 334$), the titles and abstracts of 1859 articles were screened for eligibility. Based on this first screening, a total of 1571 articles were excluded because they did not describe HLA-mediated ADRs, were non-human related, discussed development of new assays for PGx or genetic testing, were not primary literature, or were not meeting the inclusion criteria in terms of publication type. Furthermore, we had to exclude articles where we had no access to the abstract and/or the list of authors. Full text screening was performed for 288 articles, whereof 149 articles were included in the qualitative synthesis. Of the 149 articles, 27 were GWAS, whereas the other 122 were of other study types. Figure 1 depicts the flow chart describing the selection process from identification to inclusion.

**TABLE 3** Swiss drug labels mentioning HLA biomarkers

| Substance | Biomarker | Associated phenotype |
|---|---|---|
| Abacavir | HLA-B*57:01 | Abacavir hypersensitivity reaction |
| Allopurinol | HLA-B*58:01 | DRESS, SJS/TEN |
| Carbamazepine | HLA-A*31:01 | SJS/TEN, DRESS, AGEP, maculopapular rash |
| | HLA-B*15:02 | SJS/TEN |
| Flucloxacillin | HLA-B*57:01 | Increased alanine transaminase values |
| Lapatinib | HLA-DQA1*02:01 | Hepatotoxicity |
| | HLA-DRB1*07:01 | Hepatotoxicity |
| Oxcarbazepine | HLA-B*15:02 | SJS/TEN |
| | HLA-A*31:01 | SJS/TEN, DRESS, AGEP, maculopapular rash |
| Pazopanib | HLA-B*57:01 | Hepatotoxicity |
| Phenytoin | HLA-B*15:02 | SJS/TEN |

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

## Characteristics of the publications included in literature search

Of the 149 articles included in the scoping review, 76 were case-control studies, 19 were PGx analyses, 16 were case reports, and 6 were cohort studies; one study was randomized and double-blinded and two were exploratory studies. Another two articles were a combination of PGx analysis and case-control study. In total, 27 GWASs were included in the qualitative synthesis. Of these studies, 11 confirmed the results of their GWAS by an additional study (8 conducted a case-control study, 1 a cohort study, and 2 a PGx analysis).

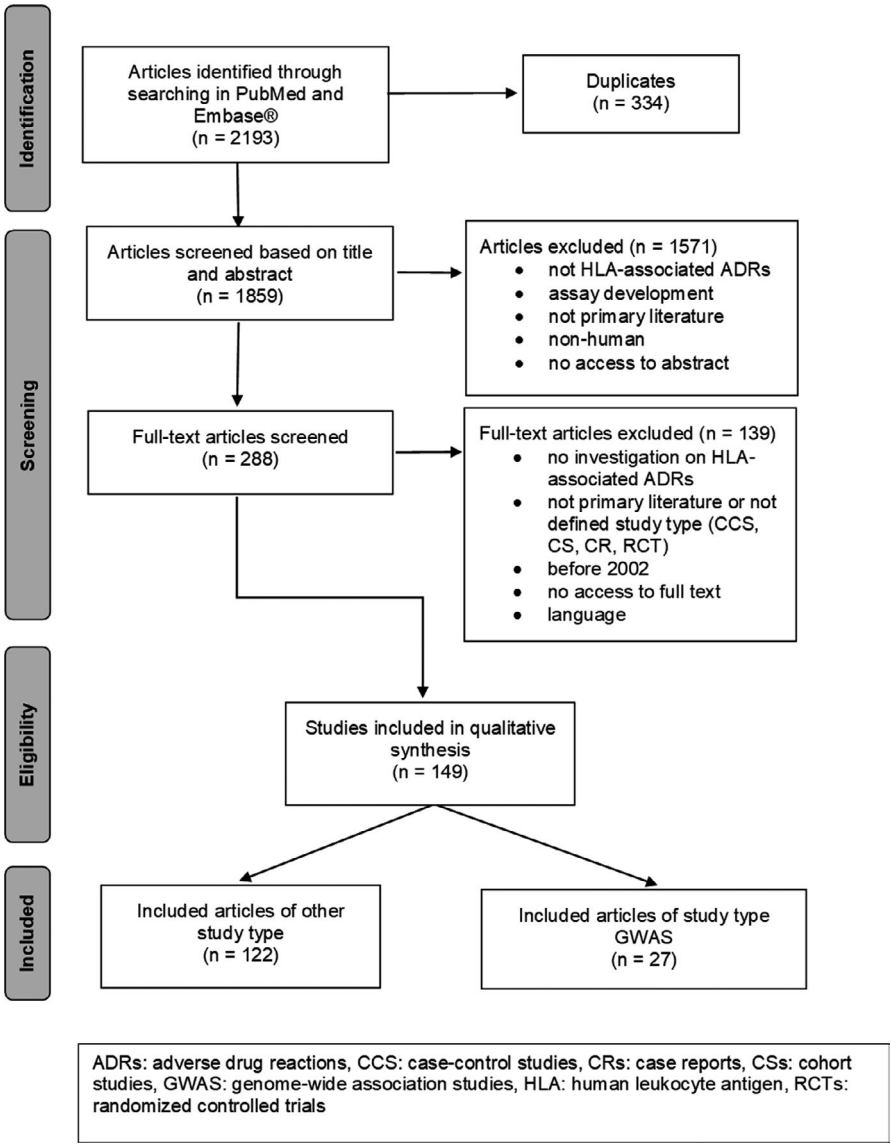


**FIGURE 1** Flow chart of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) scoping review

## Results of publications

Table S2 PRISMA Scoping Review gives details on the identified studies. In detail, the literature search provided results on HLA-associations for 26 substances and 7 substance groups (HMG-CoA reductase inhibitors, thyreostatics, beta-lactam antibiotics, agents for the treatment of tuberculosis, pyrimidine analogues, anti-epileptic drugs, and cold medicines). The raw data of all extracted studies are summarized in Table S1 Raw Data.

## Synthesis of results

Overall, the association of carbamazepine-induced cutaneous drug reactions with HLA-B*15:02 was most frequently reported ($n = 33$), followed by allopurinol and HLA-B*58:01 allele-mediated cutaneous ADRs ($n = 17$), and by abacavir and HLA-B*57:01 allele-mediated hypersensitivity reactions ($n = 16$). Studies that confirmed the association of HLA-A*31:01 in carbamazepine-induced ADRs ($n = 10$) as well as oxcarbazepine-induced ADRs were also frequent, but the latter drug was investigated in only two studies. The associations of HLA-B*15:02 and phenytoin-($n = 10$) as well as oxcarbazepine-induced ($n = 4$) cutaneous ADRs were also found. See Table S2 PRISMA Scoping Review for references.

The involvement of HLA-DRB1*0701 and HLA-DQA1*0201 in lapatinib-induced hepatotoxicity was investigated and confirmed in three studies.[26–28] Only one study[29] investigated the involvement of HLA-B*57:01 in pazopanib-induced ADRs. One GWAS investigated the involvement of HLA alleles in patients treated with flucloxacillin,[30] where the associations of HLA-B*57:01 and HLA-B*57:03 were found and confirmed. Consequently, the majority of the found literature represents knowledge on HLA-associated ADRs that has already been found its way into the DLs (see Table 3). Based on this literature search, the anatomic groups, J Antiinfectives for systemic use (6 substances and 2 substance groups), L

Antineoplastic and immunomodulating agents (6 substances and 2 substance groups), and N nervous system (7 substances and 1 substance group) contain most of the substances currently investigated for the association of HLA alleles with ADRs (see Table S2 PRISMA Scoping Review).

The literature search included many further HLA allele associations with ADRs, which are not yet addressed in the DLs. Starting from 5-amino-salicylic-acid associated with nephrotoxicity in HLA-DRB1*03:01,[31] ending with cold medicine associated to ADRs, such as SJS and TEN, combined with severe ocular complications.[32–36] HLA alleles were also associated with nevirapine-induced rash or terbinafine-induced hepatotoxicity. In detail, HLA-B*35:05[37–39] and HLA-C*04:01[40,41] showed an association with rash in nevirapine-treated patients. Moreover, in one study, HLA-DRB1*01[41] was associated with nevirapine-induced hepatotoxicity, whereas in another study the HLA-DRB1*0101 allele was not involved in "global toxicity" of nevirapine.[42] In terbinafine-treated patients with DILI, the alleles HLA-A*33:01[43,44] and HLA-A*33:03[39] as well as the haplotypes HLA-A*33:01-B*14:02-C*0802[43] and HLA-A*33:01-B*14:02-C*08:02[39] were shown to be associated with hepatotoxicity.

The clozapine-induced agranulocytosis was focus of three GWASs reporting an association with the region of HLA-B,[45,46] or HLA-DQB1.[47] Besides, the association of two different HLA-B alleles (HLA-B*57[48] and HLA-B*59:01[49]) and HLA-DRB5*02:01[48] with clozapine-induced agranulocytosis was shown in two studies. Testing the association of seven selected HLA alleles to clozapine-induced myocarditis, Lacaze et al.[50] found that six of the investigated alleles were rather protective.

Finally, antibiotics have been investigated for an association of HLA alleles with ADRs, namely beta-lactam antibiotics,[51,52] metronidazole,[53] and cotrimoxazole. The latter was investigated in three studies[54–56] testing several HLA-alleles for an association with cotrimoxazole-induced skin injuries (DISI) or SJS/TEN. Furthermore, metronidazole was found to be significantly associated with cutaneous ADRs (cADRs) in carriers of HLA-A*24:01.[53]

HLA-alleles show differences in terms of frequency in different populations.[57] Overall, the most studied population for HLA-associated ADRs were Asians ($n$ = 84, 56%), followed by Whites (29, 19%), Africans (4, 3%), American Indians (2, 1%), and Pacific Islands (2, 1%). Moreover, there were mixed populations (14, 9%), or studies where ethnicity was not specified (13, 9%).

## DISCUSSION

The methodologic approach of a scoping review was applied to generate an overview of studies reporting on HLA-associated ADRs. In our summary, we included all 149 studies that met the search criteria and were not excluded (compare Table 1). Importantly, we did not actively modify the resulting study selection even if we were made aware during our peer review, that some of the studies considered important in the field are not included in the data extraction. Notably, we restricted our literature search to small molecules, because knowledge on the PGx of biologics and other protein-derived substances is still limited. However, the limitation to drugs currently approved at the Swiss market resulted in the active exclusion of studies on dapsone, ximelagatran, ticlopidine, stavidine, lomefloxacin, and flupirtine.

The 149 studies included in the scoping review reported on 26 substances or 7 substance groups (HMG-CoA reductase inhibitors, thyreostatics, betalactam antibiotics, agents for the treatment of tuberculosis, pyrimidine analogues, antiepileptic drugs, and cold medicine) as indicated by the ATC code. The descriptive summary of the 149 studies revealed a large heterogeneity in terms of used definitions for the ADRs, examined HLA alleles, number and origin of study participants, and study types. HLA alleles were associated with an increased risk for ADRs, no association with the ADR, or were reported to be protective (reducing the risk for the ADR). Given the prevailing complexity and uncertainty, a few reflections should be made.

All of the substances identified in our analysis of the Swiss DLs mentioning HLA risk alleles (see Table 3), also appeared in the studies gathered within the literature search. However, the literature search also revealed HLA allele associations of substances that were not expected based on the analysis of the Swiss DLs. One example is terbinafine; this antimycotic was reported to be associated with hepatotoxicity in carriers of HLA-A*33:01, HLA-A*33:03, and HLA-A*33:01-B*14:02-C*080.[43,44] In contrast, for flucloxacillin, the HLA risk allele HLA-B*57:01 is mentioned in the Swiss DL,[58] yet explicitly recommending not to test prior to use. However, only one study (a GWAS with confirmatory case control study [CCS]) in our literature search reported on its association with DILI.[30] Surprisingly, also over-the-counter drugs, such as acetaminophen, appeared in the literature search.[36]

It seems important to mention that there are multiple factors influencing the recommendation for HLA-typing prior to drug use. One factor is certainly the frequency of the ADR. Flucloxacillin-induced liver injury is very rare and according to Alfirevic et al.,[59] the number needed to genotype is 13,500 to prevent one case. Nevertheless, reactive PGx testing could be affected to exclude random DILI; this is possible due to the high negative predictive value of the respective HLA-test. Considering that flucloxacillin is an antibiotic with a currently increasing use in primary care, this could be of advantage.[59,60]

HLA-B*15:02 was the most frequently investigated HLA allele. The association with ADRs induced by carbamazepine

has been confirmed in many Asian populations.[61–69] However, for other drugs (e.g., phenytoin), the ADRs could not be directly connected to a specific HLA allele but rather multiple influencing HLA alleles.[20,61,70–74]

Suggesting HLA alleles as biomarkers for an ADR, one has to consider that there may be multiple HLA alleles with influence on the therapeutic outcome. One example is allopurinol, where not only the confirmed risk allele HLA-B*58:01, but also the HLA-Cw*0302 allele is considered an HLA risk allele for severe cutaneous adverse reactions (SCAR).[75] The notion of multiple HLA alleles influencing the risk for certain ADRs, has already been put forward by Alfirevic et al. who are suggesting an "HLA panel."[59] Su et al. even went a step further and were able to show that a so-called multiplex genetic test combining HLA risk alleles and CYP2C9 substantially increases the outcome (combined sensitivity 64.7%; combined specificity 71.9%) in the prevention of phenytoin hypersensitivity reactions in Asian populations.[70] In terms of combined genotypes, Ueta et al. described the additive effect of HLA-A*02:06 and PTGER3 (prostaglandin E receptor 3) polymorphism for SJS/TEN with severe ocular complications.[32]

Importantly, the presence of a certain HLA allele cannot only increase the risk of an ADR but can also be protective. One example would be carbamazepine where in addition to the risk alleles (HLA-B*15:02, HLA-A*31:01) several HLA alleles (e.g., HLA-B*40:01, HLA-Cw*01:02, and HLA-DRB1*04:05 for SJS/TEN,[76] HLA-B*15:01 for SJS/TEN, HLA-B*40:01 for SJS/TEN and DRESS,[77] HLA-B*46:01 for SCARs[68]) were reported to reduce the risk for the ADR. These alleles are considered protective. Protective alleles have also been reported for beta-lactam antibiotics,[51] cotrimoxazole,[56] cold medicines,[35] acetaminophen,[36] and clozapine.[50] Taken together, a panel of several HLA alleles would have to be applied in order to predict the risk of ADRs for most substances. However, considering that there are risk alleles and protective alleles, which may be present at the same time in the same patient, will certainly challenge the translation in concise recommendations for HCPs.

The studies included in our scoping review investigated many various HLA-associated ADRs. HLA-associated ADRs are versatile and present in different phenotypes. Especially for cADRs, it is extremely difficult to decide whether the investigators are reporting on the same manifestation or a different one, as in many cases there is no clear definition of the phenotype. For allopurinol, an association of the HLA-B*58:01 was investigated for the following cutaneous manifestations: SJS/TEN, SCARs, DIHS, cADRs, MPE, and DRESS. Moreover, for lamotrigine different alleles were tested for association with SJS/TEN, hypersensitivity reaction, cADRs, MPE, SCARs, and DRESS. Looking at these examples, it may be hypothesized that the high amount of different cutaneous manifestations results from different definitions. The Phenotype Standardization Project[24] supports streamlining definitions in order to have more coherent phenotypes and thereby an international harmonization. In addition to harmonized phenotype definitions, the independent clinical confirmation of an ADR phenotype appears very important.

Looking at the included study types, the PREDICT-1 study[18] investigating HLAassociated ADRs for abacavir was the only RCT. This was also the first study revealing that HLA-typing could help to reduce ADRs. Except from the PREDICT-1 study, all the other HLA-associated ADRs were investigated in retrospective studies (CCSs, cohort studies, PGx analysis, etc.) where the testing was performed after manifestation of ADR. A CCS is a reasonable study design to confirm associations of HLA alleles with certain ADRs. However, in retrospective studies, one has to consider the bias of potentially including incorrectly diagnosed cases as it is extremely difficult to validate the ADR retrospectively. Accordingly, a confirmation of the clinical diagnosis can rarely be performed. In the end, this poses the danger of overestimating the prevalence of an ADR. Furthermore, our literature search also included a substantial number of GWAS, which shows the importance of this study type in PGx. We think that GWAS with focus on the HLA region are a good approach to obtain unbiased evidence on potential associations in patients with ADRs. In total, 15 case reports (thereof 6 for carbamazepine) were included in our literature search, most of them describing the case of a single patient. Even if case reports provide low to no evidence for hereditable factors contributing to the susceptibility, they can help to discover underlying mechanisms, especially if the ADR is rare (rare genetic variant) and/or if the drug is given to a small number of patients (rare disease). The genotype reported in a single case can be basis for further analyses in CCSs.

We should discuss the wide range of the number of study participants. For abacavir, carbamazepine, and allopurinol, the number of study participants ranged from 3 to 842, from 2 to 949, and from 1 to 3000, respectively. Furthermore, most studies were investigating defined subpopulations. Asians were most frequently the population, where HLA-associated ADRs were reported. Accordingly, HLA-typing and corresponding prescribing changes is warranted in Asian populations.[78] Other populations were Whites and Africans, and some studies investigated mixed populations. Interestingly, for more than 9% of the studies, ethnicity was not defined. The frequency of a certain risk allele depends on the population. Accordingly, the findings of the studies cannot be generalized, but should be interpreted respecting the specific population. Therefore, specific knowledge on the study population should be taken into account; even if this increases the complexity.

Speaking of study types, we should not forget publication bias. As it might be the case for flucloxacillin, many

associations with a low allele prevalence and/or a non-severe ADR, are likely not to be reported in the literature. Furthermore, the general bias in empirical studies has previously been discussed by Joensen et al.[79] In their work, the authors associated specific genes to adverse events of methylphenidate. In contrast to our work, they conducted a systematic review of nine studies, and also addressed the different applied definitions of ADRs together with other limitations on the ADRs (prevalence, seriousness, type, causality, and evaluation). This once more shows the advantages of a scoping review, as a systematic review seems premature at the current state of evidence. In our work, the objective was not to find out the clinical relevance of the HLA-associated ADRs, but to see which associations have been described in literature until the moment conducting the search.

However, we were not able to directly compare values, such as the positive and the negative predictive value (PPV and NPV), sensitivity, specificity, and OR. This is as some of the NPVs and PPVs have been calculated in the original studies directly from case-control data without correction for the real population prevalence of the drug hypersensitivity leading to a substantial risk of overestimation of the PPV and underestimation of the NPV. Nevertheless, we would like to discuss the clinical validity of PGx testing and take up the discussion of Tonk et al.[80]

We will base the following on the example of lapatinib, where the presence of HLA-DRB1*0701 has a high NPV, but only a moderate PPV.[26] Essentially, the majority of the individuals who experience serious lapatinib-induced liver injuries carry the allele, but the majority of HLA-DRB1*0701 allele carriers will not experience liver injuries.[27] Looking at the illustrative example of lapatinib, makes us come to an important reasoning: The clinical validity of HLA-typing does not only depend on the association of the HLA risk allele and the ADR, but also on the frequency of the HLA risk allele and the frequency of the ADR. Furthermore, for evaluation of the clinical relevance, the severity of the ADR should also be considered. In addition, one should consider that if HLA-typing is included in therapeutic decision on a drug, where the frequency of the HLA risk allele is higher than the frequency of the ADR there may be patients excluded from a therapy even if they would not experience the ADR. For the application in clinical practice, this means that even if a test seems of clinical utility, this is not necessarily the case. Therefore, we need to balance the frequency of the HLA risk allele against the frequency of use in practice, and measure clinical validity to know how to interpret PGx testing.[80] Manson et al. effected a systematic review on diagnostic criteria for HLA-typing to prevent ADRs. The tests were almost all highly specific and had a high NPV; however, the sensitivity of HLA-typing showed wide ranges from 0% to 100%. Moreover, with exception of HLA-typing for abacavir hypersensitivity, the positive predictive value was low.[81] More studies are needed to evaluate diagnostic test criteria.

To assemble the necessary evidence for an association of HLA alleles and ADRs, studies with sufficient participants in mixed populations designed as large prospective studies are needed. This is not limited to HLA but also affects the implementation of pharmacogenotyping in patient care. Although RCTs are the gold standard for the comparison of two interventions, it can be questioned whether RCTs are the only way to establish the value of PGx. However, even if there is a mechanistic link supporting PGx findings influencing patient outcome, and even if there are guidelines translating these findings in clinical recommendations, the implementation of PGx testing in clinical practice is often questioned due to the lack of data from RCTs.

## CONCLUSION

The scoping review identified a considerable number of studies that investigated various substances, HLA alleles, and associated ADRs. It became clear that pre-emptive testing of HLA alleles (HLA-typing) may have a potential; however, it is not possible to derive the actual clinical relevance from these studies. The overview of HLA-associated ADRs ranged from poor to strong available evidence, whereby revealing a prevailing complexity and uncertainty. Screening the different factors influencing the HLA-associated ADRs helped to identify the basic points for further investigations in the field of HLA-associated ADRs. That is to say, previously confirmed associations, where more evidence needs to be generated, potential protective alleles to further explore, or also negative associations that can be excluded in a future systematic analysis in order to receive comprehensible data of good quality and validity. Thus, for the future consistent definitions on the different phenotypes need to be established and applied and the reporting of association studies should follow a harmonized structure.

### CONFLICT OF INTERESTS

All authors declared no competing interests for this work.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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