



Role of pharmacogenomics in T-cell hypersensitivity drug reactions

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Purpose of review

An update of the pharmacogenetic risk factors associated with T-cell-mediated delayed hypersensitivity reactions.

Recent findings

Recent HLA associations relevant to our understanding of immunopathogenesis and clinical practice include HLA-B*13:01 with co-trimoxazole-induced SCAR, and HLA-A*32:01 with vancomycin-DRESS, for which an extended HLA class II haplotype is implicated in glycopeptide antibiotic cross-reactivity. Hypoactive variants of ERAP1, an enzyme-trimming peptide prior to HLA loading, are now associated with protection from abacavir-hypersensitivity in HLA-B*57:01+ patients, and single-cell sequencing has defined the skin-restricted expansion of a single, public and drug-reactive dominant TCR across patients with HLA-B*15:02-restricted carbamazepine-induced SJS/TEN. More recent strategies for the use of HLA and other risk factors may include risk-stratification, early diagnosis, and diagnosis in addition to screening.

Summary

HLA is necessary but insufficient as a risk factor for the development of most T-cell-mediated reactions. Newly emerged genetic and ecological risk factors, combined with HLA-restricted response, align with underlying immunopathogenesis and drive towards enhanced strategies to improve positive-predictive and negative-predictive values. With large population-matched cohorts, genetic studies typically focus on populations that have been readily accessible to research studies, but it is now imperative to address similar risk in globally relevant and understudied populations.

Keywords

delayed drug hypersensitivity, endoplasmic reticulum aminopeptidase, genetic risk predisposition, human leukocyte antigen, T-cell receptor

INTRODUCTION

Delayed hypersensitivity reactions (DHR), which most often manifest in skin, are well documented as T-cell mediated, with both drug-responsive and metabolite-responsive T cells isolated from the blood and skin of patients. Of the associated clinically diverse severe cutaneous adverse reactions (SCAR), the most severe is Stevens Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN), associated with drug-induced keratinocyte death, cutaneous blistering, epidermal detachment, and average 30% mortality [1]. Moreover, T cells similarly attack different mucous membranes, driving morbidities in survivors including blindness, reproductive, and mental health problems. Although disease is partially determined by drug-specific factors, reactions remain rare, occurring in an estimated 1–5/1 000 000 patients [1]. Thus, combined

with a lack of suitably reflective animal models, these life-threatening reactions are neither typically observed during preclinical screening, nor clinical trials, and only become evident once drugs are marketed for use in general population. Although recent strong associations with human leukocyte antigen (HLA) class I alleles and severe T-cell-mediated DHR have been promising, the positive-predictive value (PPV) for most reactions is less than 5%

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KEY POINTS

- Specific HLA alleles are major risk factors for DHR but are often drug, reaction, and population-specific.
- Ecological and genetic factors may explain the positive-predictive value gap.
- Proteomic strategies have characterized the HLA-presented immunopeptidome, critical to understand shared HLA-binding specificities and predict risk across populations.
- The HLA-presented immunopeptidome is skewed by hyporeactive/hyperactive allotypes of ERAP, which trim peptides to optimal length for HLA loading and predispose risk.
- Single-cell sequencing characterizes the complete dominant, risk-HLA restricted drug-reactive TCR in the blister fluid of SJS/TEN, which in the case of HLA-B*15:02-restricted carbamazepine-induced SJS/TEN appears to be a public clonotype.

whilst the negative-predictive value (NPV) remains incomplete, limiting utility of HLA screening as a preventive strategy for most drugs. In this review, we discuss the role of pharmacogenomics in prediction and prevention, early diagnosis, and understanding of disease immunopathogenesis.

SURFACE ANTIGEN PRESENTATION: HUMAN LEUKOCYTE ANTIGEN ALLELES

Discovery of significant association between HLA-B*57:01 and abacavir-hypersensitivity syndrome was crucial to our understanding of DHR immunopathogenesis (Fig. 1). Subsequently, HLA-B*57:01 testing prior to abacavir prescription became the standard of care in the developed world [2,3] and this seminal discovery began the now almost 20 years of risk HLA discovery for different DHRs, including SJS/TEN, drug reaction with eosinophilia and systemic symptoms (DRESS), and drug-induced liver injury (DILI). However, despite global prevalence of drug-specific DHR, HLA alleles show divergence in global population carriage (Table 1), implicating a role for different alleles to drive disease in different populations. Indeed SJS/TEN induced by carbamazepine is strongly associated with HLA-B*15:02, with preventive screening active in countries with high allelic prevalence including Taiwan and Hong Kong [4]. However, European, and African populations have carriage of less than 1%, demonstrating the importance of performing HLA association studies with population-matched controls across diverse populations. New associations continue to be uncovered, in part driven by increased

use of advanced platforms, such as whole genome sequencing (WGS). In 2020, Wang used WGS to identify association between co-trimoxazole (sulfamethoxazole-trimethoprim)-induced SCAR and single nucleotide polymorphism (SNP) rs41554616 in patients from Taiwan, Thailand, and Malaysia [5[□]]. With the SNP near the HLA-B locus, subsequent HLA-typing discovered association with HLA-B*13:01, an allele in strong linkage disequilibrium. With complexity of allelic associations in linkage disequilibrium, functional validation is critical to confirm HLA restriction and culprit antigen reactivity. The authors use in-silico modelling to demonstrate likely HLA-B*13:01-interaction with sulfamethoxazole and the reactive metabolite 4-nitro sulfamethoxazole, and also, albeit through different binding pockets, trimethoprim, and the structurally similar and SCAR-associated antibiotic, dapsone. To confirm culprit-antigen reactivity, the authors use an in-vitro lymphocyte activation assay to show restricted activation by the sulphonamide component, with dapsone cross-reactivity, but without activation by trimethoprim [5[□]]. In 2020, Suksem *et al.* [6[□]] also reported similar risk with co-trimoxazole-induced SCAR in Thai patients, demonstrating significant association with HLA-B*15:02/HLA-C*08:01 and HLA-B*13:01 for SJS/TEN and DRESS, respectively.

In 2019, Konvinse *et al.* [7[□]] reported strong association between HLA-A*32:01 and vancomycin-induced DRESS. A time-to-event analysis suggested that 20% of HLA-A*32:01 patients would develop vancomycin DRESS if exposed for two or more weeks. As DRESS has a latency of 2–8 weeks, this creates a clinical window for HLA-A*32:01 typing to preemptively stratify patients according to risk. An inexpensive and cost-effective test to facilitate such strategy was recently developed by Rwandamuriye *et al.* [8[□]]. In 2020, Nakkam *et al.* reported cross-reactivity of alternate glycopeptide antibiotics teicoplanin and telavancin in patients with HLA-A*32:01-restricted vancomycin-DRESS, who share expression of an HLA class II, DQA1*01:01, DQB1*05:03 haplotype [9[□]]. Virtual docking suggested likely interaction of these drugs with these class II alleles, suggesting that while HLA-A*32:01 may predispose risk to vancomycin, extended HLA class II risk may predispose cross-reactivity [9[□]].

SURFACE ANTIGEN PRESENTATION: HUMAN LEUKOCYTE ANTIGEN-INTERACTING IMMUNOGENIC STRUCTURES

Traditionally, three models postulate T-cell activation by drugs [10]: haptenization where drug-antigen

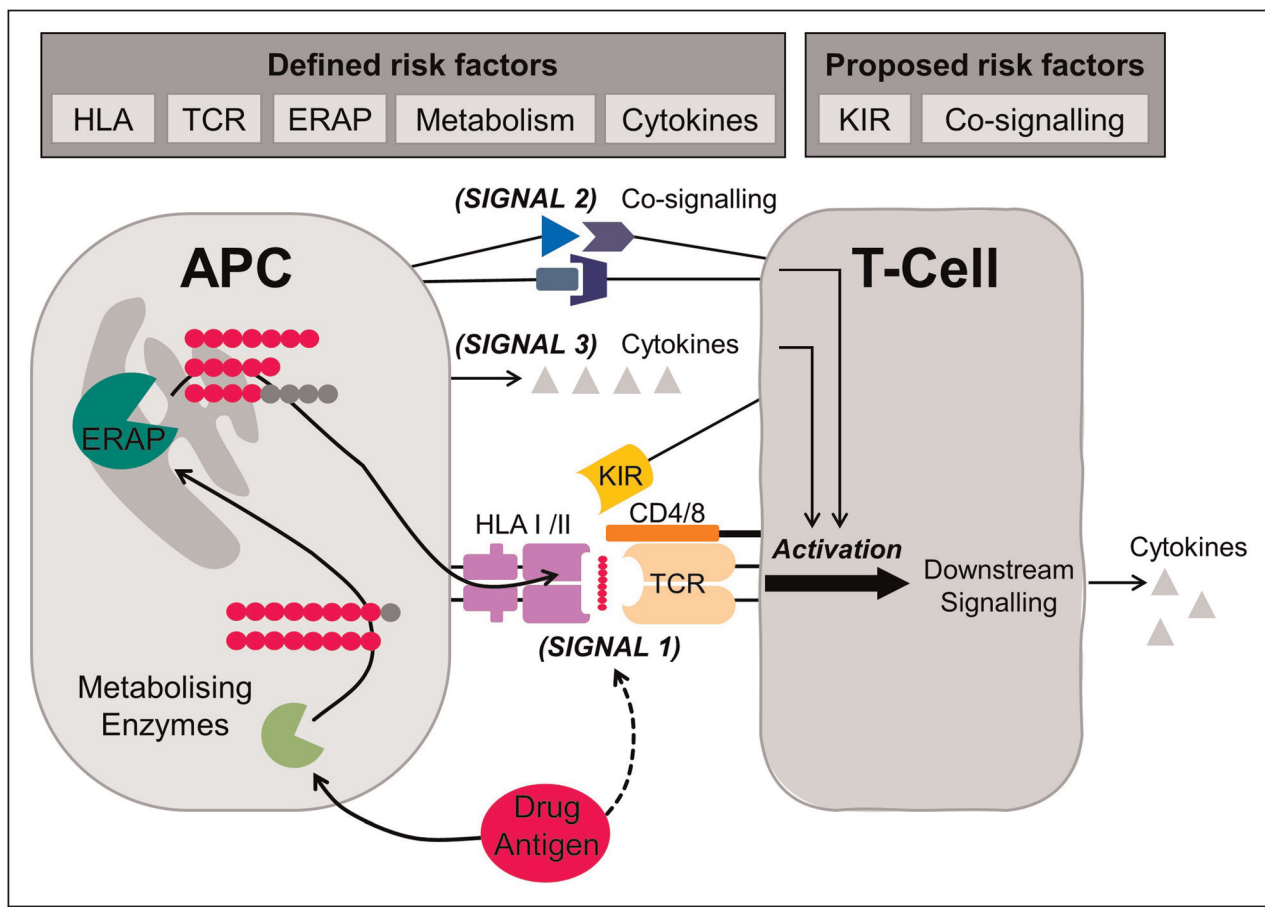


FIGURE 1. Cellular interaction of pharmacogenetic risk factors associated with predisposition to delayed drug hypersensitivity reactions. Drug or drug-derived antigen may bind to human leukocyte antigen directly or undergo metabolism and cellular processing to peptides, which undergo N-terminal trimming by ERAP before loading onto HLA for presentation to corresponding TCR (signal 1) at the cell surface. T cells also express KIR, which may bind to HLA to regulate drug-induced cytotoxic degranulation, which is also regulated by co-signalling (signal 2) pathways, with summative co-stimulation or co-inhibition driving cytotoxic degranulation and pro-inflammatory cytokine release or tolerance with anti-inflammatory cytokine release, respectively. Cytokines are also released from antigen-presenting cells to polarize T-cell differentiation (signal 3). APC, antigen-presenting cell; ERAP, endoplasmic reticulum aminopeptidase; HLA, human leukocyte antigen; KIR, killer-like immunoglobulin receptor; TCR, T-cell receptor.

bound to protein is recognized as neoantigen, direct pharmacological interaction (P-I) where drug-antigen directly stimulates T cells, and the altered peptide repertoire hypothesis whereby drug-antigen modifies the HLA-binding groove such that different self-peptides bind that are not usually associated and thus deemed immunogenic. Evidence of the latter exists for abacavir, which binds within the antigen-binding cleft of HLA-B*57:01, to favour presentation of peptides with a linear aliphatic C-terminal residue, such as valine and isoleucine over the usual cyclic hydrophobic C-terminal residues [11]. Polyclonal response to abacavir in positive patch test is also supportive of this phenomenon [12].

It may be that diverse HLA respond to the same drug because of similar binding pockets or anchor residues, an understanding of which will propose

risk across populations. To date, this is exemplified by multiallelic restriction for nevirapine, a nonnucleoside reverse transcriptase inhibitor still used in the developing world as first-line treatment of HIV. Specifically, a unique F pocket in the HLA-binding groove shared by different HLA-C*04 alleles enables nevirapine to bind HLA-C*04:01, HLA-C*05:01, and HLA-C*18:01 [13]. Such approach is suited to drugs that act via direct pharmacological interaction as there is a requirement to understand the immunogenic chemical structure. However, there have been recent efforts to understand similar binding where drug-peptides or self-peptides are likely to drive response. In one strategy, Tailor *et al.* demonstrates utility of designer amoxicillin-modified HLA-binding peptides to determine the relevant point of lysine modification by drug for risk presentation

Table 1. Divergent population carriage of strongly predictive human leukocyte antigen risk alleles associated with drug-induced hypersensitivity reactions

Drug reaction	Risk allele	Population	Allele frequency (%)
Abacavir-HSR	B*57:01	Han Chinese	1–4.5
		European	5–8
		African American	0.3–2
		Japanese	<0.01
		Indigenous Australian	0.7–1.5
Allopurinol-SJS/TEN	B*58:01	Han Chinese	2–17
		European	1–6
		African American	2.6–6.4
		Japanese	0.5
		Indigenous Australian	1
Carbamazepine-SJS/TEN	B*15:02	Han Chinese	1.5–7.3
		European	<0.1
		African American	0–1
		Japanese	0.03–0.1
		Indigenous Australian	0.7
Dapsone-HSR	B*13:01	Han Chinese	2–6
		European	0–1.2
		African American	<0.04
		Japanese	0–1.5
		Indigenous Australian	13–27
Nevirapine-SJS/TEN	C*04:01	Han Chinese	5.6–10
		European	4.5–19.3
		African American	15.7–22.8
		Japanese	3.6–6.5
		Indigenous Australian	17.9–27.5
Vancomycin-DRESS	A*32:01	Han Chinese	0.8–2.4
		European	0.6–10
		African American	2
		Japanese	0.02
		Indigenous Australian	0.3–2

Population carriage as reported by allelefrequencies.net.

by HLA-DRB1*15:01-DQB1*06:02 haplotype alleles [14²²]. As the protein(s) origins of drug haptens remain unknown, nonspecific peptides were created from a poly-alanine backbone with inclusion of key anchor residues for target risk HLA interactions. Importantly, although previous studies have failed to identify drug-responsive CD4⁺ T cells relevant to DILI, peptides incorporating lysine to allow amoxicillin binding at peptide positions 2 and 3, but not 5 and 6, stimulated patient-derived T-cell clones. These data detail the likely point of haptenization on HLA-binding peptides relevant to reaction [14²²].

Although this synthetic approach incorporates anchor residues to mimic natural peptides, Waddington *et al.* [15²²] used in-vitro culture and mass spectrometry to elute and fully-annotate six

naturally processed flucloxacillin-modified peptides from the ligandome of risk HLA-B*57:01-expressing antigen-presenting cells. The authors draw attention to a comparative lack of sensitivity by characterizing drug-modified peptides in cell lysate, as only a minority (<0.1%) will be presented by the risk HLA allele. Importantly, similar flucloxacillin modifications within the HLA-B57:01 immunopeptidome are described by Puig *et al.* [16²²], including those derived from high abundance KAAKLKEY and RTKKVGIVGKY sequences from the high mobility group HMGB-1 protein and 60S ribosomal protein, respectively, but with restricted modification at position 4. Puig *et al.* [16²²] also reported a flucloxacillin-modified HLA-derived peptide and utilized a transgenic HLA-B*57:01-expressing mouse

model to validate the comparative immunogenicity of described adducts.

In contrast, Thomson *et al.* [17²²] demonstrates the alternative approach, creating abacavir analogues, modified by the 6-amino cyclopropyl group, which binds in the F-pocket of HLA-B*57:01, to screen for reduced T-cell immunogenicity but maintained therapeutic efficacy. Although drug re-design would be an expensive approach, this study demonstrates ability to screen out structural immunogenicity.

ANTIGEN AVAILABILITY: ROLE OF METABOLISM AND PREHUMAN LEUKOCYTE ANTIGEN PEPTIDE-PROCESSING

Drug metabolism is a complex process often mediated by more than one enzyme. While the ultimate goal is a product suitable for excretion, intermediates hold potential to form immunogenic moieties, which may be too unstable for synthesis to assess immunogenicity *in vitro*. Importantly, while drug metabolising enzymes may be highly polymorphic, with ultrarapid to poor function variants of various cytochrome P450 (CYP450) enzymes [18], few to date have been associated with DHRs. The antiepileptic phenytoin is an exception, predominantly eliminated via hydroxylation by CYP2C9, an enzyme for which the *2 and *3 variants have reduced function. Studies have shown that poor CYP2C9*3-mediated phenytoin metabolism reduces phenytoin clearance and is associated with increased risk of maculopapular exanthema (MPE) and SCAR in South East Asian, Japanese, and Malaysian populations [19]. As such, the *Clinical Pharmacogenetics Implementation Consortium* released updated 2020 guidelines for Phenytoin Dosing, reinforcing recommended administration of a 25% or 50% reduced starting maintenance dose for CYP2C9 intermediate and poor metabolisers, respectively [20]. Despite a handful of other weak associations, drug/drug metabolite plasma concentration is not a key determinant in DHR susceptibility, nor the mere presence of protein adducts. Meng found that all patients exposed to piperacillin possessed protein adducts at a threshold capable of activating T-cells, regardless of whether they developed hypersensitivity or remained tolerant [21]. However recent data suggests influence of downstream N-terminal peptide processing efficiencies to skew the HLA-presented immunopeptidome, a process driven by endoplasmic reticulum aminopeptidases (ERAP) 1 and 2 [22] (Fig. 1). Specifically, Pavlos reported association between ERAP1 allotypes with reduced trimming efficiency, and tolerance in abacavir-

exposed HLA-B*57:01+ patients [23²³]. However, even with formation of an immunogenic risk HLA-antigen complex, only select T-cells are activated suggesting availability of antigen-reactive T-cells may also restrict response. A recent mouse model supports potential importance of CD4+ T cells in mediating tolerance to the altered peptide repertoire induced by abacavir and in suppressing maturation of dendritic cells. CD4+ T cell depletion that occurs in the setting of HIV may be important to explain this break in tolerance [24,25].

T-CELL SPECIFICITY: T-CELL RECEPTOR RECOGNITION OF HUMAN LEUKOCYTE ANTIGEN

Activation of T cells requires stable interaction between HLA, antigen, and T-cell receptor (TCR); a complex called signal 1 (Fig. 1). Importantly, although total TCR repertoire is expansive, estimated between 10^{13} and 10^{15} TCRs [26] and driven by somatic recombination for a physiological requirement to respond to diverse antigenic peptides, distribution may be restricted with certain TCR specificities in specific tissues. For instance, tissue-resident memory T cells of skin and mucous membranes contain cells with TCR specificities for previously encountered viral antigens, positioned at these likely re-exposure sites to ensure rapid response to re-infection [27]. This dichotomic expression is particularly interesting as reasoning for why DHRs may be tissue-restricted and aligns with a heterologous immunity model that implicates reactivation of viral-primed T cells with cross-reacting drug-antigen. Importantly, if true, this is thought likely to involve common broad-exposure pathogens as abacavir-responsive T cells are identifiable in all HLA-B*57:01+ but drug-naïve individuals [28]. The best supporting evidence remains demonstrated cross-reactivity of abacavir-reactive T cells with an HSV1/2-specific VTQQAQVRL sequence [29]. Although polyclonal response is reported with abacavir, Chung *et al.* identified a preferentially expanded TCR in risk HLA-B*58:01-restricted patient blister during allopurinol-induced SCAR [30]. However, this study assessed expression of the TCR beta chain alone, yet interaction with corresponding alpha and J chains ultimately shapes complementary determining region 3 (CDR3), providing antigen specificity. In 2019, Pan *et al.* [31²⁴] provided the first complete drug-antigen reactive TCR for DHR. Specifically, comparing single-cell sequencing of blister fluid from HLA-B*15:02+ carbamazepine-SJS/TEN patients, Pan identified a dominant TCR with 'VFDNTDKLI' TCR α CDR3 and 'ASSLAGELFF' TCR β CDR3, but which was absent from tolerant controls. Critically, functional studies in a transgenic mouse model confirmed HLA-B*15:02-

restricted reactivity of this public TCR clonotype with carbamazepine [31²²].

INFLAMMATORY RESPONSE: CYTOKINE VARIANTS

Cytokines are signalling molecules in DHRs that either polarize T-cell differentiation after release from antigen-presenting cells, with resulting extracellular milieu defined as T-cell activation signal 3, or act to exert pro-inflammatory and anti-inflammatory effects after release from activated T cells (Fig. 1). Although cytokine variants are associated with immediate drug hypersensitivities, there remain limited associations with T-cell-mediated DHRs. However, cytokines can be pleiotropic and released in combination, thus individual effect may be difficult to ascertain. Significant associations to date include TNF- α polymorphism-380G/A with antituberculosis drug-induced hepatitis [32], and IL10-819 TT and IL10-592 AA with liver injury from docetaxel [33].

PROPOSED RISK: CO-SIGNALLING

Other risk factors are proposed but remain without association. One such factor is co-stimulatory and co-inhibitory receptors, collectively called co-signalling and T-cell activation ‘signal 2’, which upregulate or downregulate T-cell activation, respectively (Fig. 1). In a physiological setting, this regulatory balance directs tolerance or cytotoxic manifestation following formation of stable HLA-antigen-TCR complex, however, if a patient’s regulatory state is altered, hypersensitivity may develop to an otherwise tolerated drug [34²³,35]. Importantly, co-inhibitory immune checkpoint inhibitors (ICI) are now widely utilized in cancer immunotherapy, and while adverse reactions are common, intriguing reports describe increased hypersensitivity incidence with exposure to low-molecular-weight drugs in patients who previously received ICI [36,37]. Moreover, autoimmune diseases are associated with polymorphisms in these co-inhibitory pathways, implicating a role in inter-patient variability [38–40]. Further study is now warranted to understand the influence of checkpoint polymorphisms to regulate drug tolerance.

PROPOSED RISK: KILLER-CELL IMMUNOGLOBULIN-LIKE RECEPTORS

Killer-cell immunoglobulin receptors (KIR) are highly polymorphic ligands for HLA, which act to regulate cytotoxic degranulation by NK cells and T cells with specificity for the interacting peptide [41] (Fig. 1). Complexity of HLA interaction remains undefined, but progression of infectious disease restricted by

HLA is recently associated with specific KIR alleles [42]. Although association with DHR remains unreported, in the aforementioned study by Puig *et al.* [16²⁴] who observed modification of risk HLA lysine residues by flucloxacillin, the authors note the potential impact of such drug modification for interacting KIR. Moreover, expression of KIR2DL2 and KIR2DL3 are increased on circulating T cells during SJS/TEN, implicating specific role in disease [43]. Studies comparing drug hypersensitive and tolerant patients with well defined HLA risk are now required to determine relevance of KIR to DHR.

CONCLUSION

HLA screening is in clinical practice for abacavir and HLA-B*57:01, carbamazepine and HLA-B*15:02 or B*31:01 in patients of Asian descent, and dapsone and HLA-B*13:01 in Chinese populations [44]. For allopurinol and HLA-B*58:01, although selectively implemented in Southeast Asia, the lack of well tolerated alternatives and incomplete PPV and NPV for other populations limits translation. With large population-matched cohorts, association study-defined risk typically focusses on prevalent global populations but it is now imperative to address similar risk in minorities. Strategies include in-vitro functional or in-silico modelling of similar drug–HLA binding [13], or careful clinical clustering in specific ethnic populations [45²⁵]. New pharmacogenetic risk factors include specificity of corresponding TCR and functional trimming capacity of ERAP allotypes, which drive towards cost-beneficial strategies for risk prevention. However, significant challenges remain, including means to define HLA-interacting immunogenic peptides, and the influence of regulatory determinants. Importantly, regulation is dynamic, driven by ecological exposures, such as ICI, imparting both interindividual and intra-individual susceptibilities. Critically, technological advancements now enable whole genome sequencing and single-cell characterization for integrated multiomic approaches to dissect multifaceted risk signatures. High-throughput epitope-screening techniques that utilize the dominant TCR from skin or blister could be useful to confirm drug-specific HLA restriction.

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Conflicts of interest

E.J.P. is co-director of IID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity and holds a patent for detection of HLA-A*32:01 in connection with diagnosing DRESS without any financial remuneration. No other authors declare conflicts of interest.

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