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PharmGKB summary: very important pharmacogene information for human leukocyte antigen B

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Introduction

The human leukocyte antigen B (HLA-B) gene is a member of the major histocompatibility complex (MHC), a region of the human genome located on chromosome 6. The MHC [also known as the human leukocyte antigen (HLA) complex] includes three subregions, designated as class I, class II, and class III. Each of these subregions contains a variety of genes that mainly code for proteins involved in the immune system. HLA-B is part of the class I group, along with HLA-A and HLA-C, all three of which code for their eponymous proteins [1]. Class II genes include HLA-DR, HLA-DP, and HLA-DQ [2], and class III genes include complement components and cytokines such as complement factor B (CFB) and members of the tumor necrosis factor (TNF) family [1,3]. The MHC is a large region of the genome and contains many other genes besides the ones listed above; please see Horton et al. [1] for more details. The HLA genes are important within the field of pharmacogenetics: variations within these genes have been associated with severe drug reactions as well as changes in how well a patient responds to a drug.

The HLA-B protein and the other class I group members are cell-surface molecules responsible for the presentation of endogenous peptides to CD8 + T cells and exist on almost all nucleated cells. This is in contrast to class II molecules, which display exogenous peptides to CD4 + T cells, and are present only on antigen-presenting cells such as macrophages or dendritic cells [2,4]. This presentation of peptides to T cells aids in the recognition of pathogens [2]. As a class I molecule, most of the peptides that HLA-B presents come from the normal breakdown of host cellular proteins and are recognized by the immune system as such (i.e. 'self' peptides). However, when a cell becomes infected by a pathogen, the proteins presented will be from the pathogen and recognized as foreign or 'nonself'. T-cell antigen receptors on CD8 + cytotoxic T cells are responsible for this recognition and will stimulate an immune reaction that destroys the cell [5].

Class I molecules are expressed in a codominant manner, and humans inherit a set of HLA-A, B, and C genes from each parent. Therefore, given allelic variations within these genes, up to six different class I molecules can be expressed on a cell surface. HLA-A, B, and C are heterodimers consisting of an α chain, encoded by their respective genes, and a protein known as β2-microglobulin, which is encoded on chromosome 15. The α chain of HLA-B has four domains: one cytoplasmic, one transmembrane, one that binds to CD8 + cytotoxic T cells, and one that makes up a peptide-binding groove, where the presented peptide is nestled [5]. This peptide-binding region of the gene is highly polymorphic, and allelic differences between class I genes are often because of variations within this region [2,5]. Indeed, allelic variants of class I genes can differ from one another by up to 20 amino acids. Peptides bind to the groove through interaction with specific amino acid residues; thus, any amino acid changes because of allelic variation may affect the peptide-binding specificity of a class I molecule [5] (class II molecules have more flexibility in peptide-binding; see Janeway et al. [5]). The type of extensive polymorphism seen in HLA genes allows a wide variety of peptides to be presented, and likely evolved to combat pathogens effectively [5]. In addition to affecting the peptides capable of being presented, allelic variants in the HLA-B gene have also been associated with susceptibility and resistance to numerous diseases as well as adverse reactions to a wide range of pharmaceuticals. This makes HLA-B highly relevant to pharmacogenetic research. This Very Important Pharmacogene summary on HLA-B is available with interactive links to genetic variants and drugs on the PharmGKB website at *http://www.pharmgkb.org/gene/PA35056*.

HLA-B allele frequencies and nomenclature

Because of the highly polymorphic nature of class I genes, a large number of HLA-B alleles have been identified. Information on the frequencies of over 2800 HLA-B alleles in populations worldwide can be found at The Allele Frequency Net Database (*http://www.allelefrequencies.net/*) [6]; allele frequencies for specific polymorphisms will be discussed within relevant sections of this review. Systematic nomenclature for these alleles is

invaluable, given their quantity. The HLA nomenclature committee has provided a detailed nomenclature to this end, and comprehensive information on the allele naming process can be found at their website at *http://hla.alleles.org* [7]. Briefly, all *HLA* alleles receive at least a four-digit name consisting of two sets of two digits separated by a colon, such as *HLA-B*57:01*. The first set of digits before the colon describes the type, typically the antigen designation used to describe the *HLA* alleles before genetic sequencing. The second set of digits indicates the specific allele, numerically ordered on the basis of when the DNA sequence was discovered; this set of digits describes nonsynonymous substitutions only [7, 8]. This paper will only refer to the first one or two sets of digits. However, longer names, up to four sets of digits separated by colons and possibly a letter suffix, can be assigned if more detail is necessary, such as the type or the location of nucleotide substitution (e.g. synonymous or intronic) or resultant protein expression (e.g. null protein or cytoplasmic protein); for more information on this process, please refer to the HLA nomenclature website (*http://hla.alleles.org*).

HLA-B and disease associations

A number of *HLA-B* alleles or allele groups have been associated with susceptibility or resistance to particular diseases. These include *HLA-B*53* and resistance to malaria [9,10], *HLA-B*51*, and susceptibility to the inflammatory condition Beçhet's disease [11,12], and *HLA-B*46*, and increased risk of Graves' disease, an autoimmune disorder [13]. Two particularly strong disease associations are *HLA-B*57* and HIV long-term nonprogression, and *HLA-B*27* and ankylosing spondylitis (AS).

HLA-B*57 and HIV long-term nonprogression

Without treatment, almost all patients infected with HIV will ultimately progress to AIDS. However, a small percentage of patients do not advance, even long after the median progression time. These patients are referred to as long-term nonprogressors or 'elite controllers', and *HLA-B*57* alleles, particularly *57:01* and *57:03*, are highly enriched in this group of individuals [14–21]. Although this association is well known, the mechanism by which it occurs remains unclear. Kosmrlj and colleagues used computer algorithms to predict that less than half the number of unique peptides (derived from the human proteome) bound to the HLA-B*57:01 protein compared with HLA-B*07:01 (a non-HIV-protective form of the molecule). The authors suggested that this affected repertoire development, leading to T cells that had been exposed to fewer self-peptides. This in turn may lead to a higher frequency of T cells that recognize viral peptides, such as those from HIV, as well as T cells that are more cross-reactive toward mutant epitopes. These qualities would enable the T cells to better control

the HIV infection, keeping the viral load in check and thereby making the development of AIDS unlikely [16].

HLA-B*27 and ankylosing spondylitis

AS is a chronic inflammatory rheumatic disease, affecting mainly the axial skeleton and the sacroiliac joints. It leads to inflammatory back pain, as well as other clinical features including enthesitis and anterior uveitis [22]. The presence of *HLA-B*27* leads to the highest risk for AS, and this form of *HLA-B* is found in over 90% of AS patients with European ancestry. However, only 1–5% of *HLA-B*27* individuals will go on to develop AS, and not all alleles of *HLA-B*27* are associated with its development. Although *HLA-B*27:05, *27:02, *27:04*, and *27:07* do confer risk, other types such as *27:06* and *27:09* do not appear to be associated with the disease [23]. As with HIV and *HLA-B*57:01*, the mechanism behind this association is unclear, although multiple theories have attempted to explain the relationship. Several of these theories are summarized in a review by McHugh and Bowness [24], including the arthritogenic peptide hypothesis, which suggests that HLA-B*27 binds particular peptides that give rise to a cytotoxic T-cell response, the misfolding and unfolded protein response hypothesis, which suggests that the accumulation of abnormally folded HLA-B*27 molecules leads to an inflammatory response, and the free heavy chain and homodimer hypothesis, where AS results from the immune recognition of monomeric or dimeric β2-microglobulin-free and peptide-free HLA-B*27 molecules [24]. Recent GWAS analyses have identified a number of non-MHC genes associated with AS susceptibility; these genes may help explain the mechanism of AS pathogenesis. For example, multiple genes within the interleukin-23 (IL-23) proinflammatory cytokine pathway were associated with AS, indicating that this may be a core immunological pathway underlying disease development. In addition, multiple aminopeptidase genes, such as *ERAP1* and *ERAP2*, have been associated with AS. The protein products of these genes are involved in peptide trimming before HLA class I binding and presentation, suggesting that HLA-B*27 may be involved in disease development through the aberrant trimming or presentation of peptides [25–28].

HLA-B pharmacogenetics

HLA-B alleles have been associated with reactions to a large number of different drugs. Some of these associations have been well studied, such as *HLA-B*57:01* and abacavir hypersensitivity, *HLA-B*58:01* and allopurinol-induced severe cutaneous adverse reactions (SCARs), and *HLA-B*15:02* and carbamazepine (CBZ)-induced Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Other associations that are not as widely studied, but still show significant results include *HLA-B*57:01* and flucloxacillin-induced liver injury and *HLA-B*15:02* and phenytoin-induced SJS and TEN.

Table 1 List of _HLA-B_ alleles and their associated drug phenotypes

HLA-B risk allele	Drug	Phenotype	References	PPV (%)	NPV (%)	References
57:01	Abacavir	Hypersensitivity reaction	See Table 2	55	100	Mallal and colleagues [29,31]
	Flucloxacillin	Drug-induced liver injury	Daly et al. [30]			
58:01	Allopurinol	SCARs, MPE	See Table 3	1.5	100	Tassaneeyakul et al. [32]
15:02	Carbamazepine	SJS/TEN	See Table 4	1.8	100	Yip et al. [33]
	Phenytoin	SJS/TEN	See Table 5	33[a]	100[a]	Tassaneeyakul et al. [34]

The phenotypes listed for each drug are more likely to occur in patients who carry the associated allele. For example, carriers of *57:01* who are administered abacavir have an increased chance of a hypersensitivity reaction compared with noncarriers. When available, positive and negative predictive values are also shown. An interactive version of this table is available online at _http://www.pharmgkb.org/gene/PA35056_.
HLA, human leukocyte antigen; MPE, maculopapular eruption; NPV, negative predictive value; PPV, positive predictive value; SCARs, severe cutaneous adverse reactions; SJS/TEN, Stevens–Johnson Syndrome/toxic epidermal necrolysis.
[a]For phenytoin-induced SJS only.

A list of the _HLA-B_ alleles and pharmacogenetic associations discussed in this review (along with their positive and negative predictive values, if available) can be found in Table 1. For the alleles presented in this paper, there is no difference in phenotype depending on whether one or two _HLA-B_ alleles are present, and therefore, the pharmacogenetic studies discussed only consider whether an individual has the allele or not. Consequently, in the tables throughout this review, the 'prevalence' of an _HLA-B_ allele refers to how many patients carry that allele and not the frequency of the allele in the population. Some studies do use allele frequencies in their statistical analyses, and these cases are noted within the tables.

Many other _HLA-B_ alleles besides the ones discussed in this paper have shown associations with various drug phenotypes. A table of all the _HLA-B_ allele and drug phenotype associations currently annotated by PharmGKB can be found on the website at _http://www.pharmgkb.org/gene/PA35056_.

HLA-B testing
Several options exist for determining whether a patient carries a particular _HLA-B_ allele. One is by direct sequencing of the gene, and assignment of a star allele after checking the sequence against known _HLA-B_ alleles. Although this method provides high-resolution genotyping and is the most accurate, it is both time-consuming and expensive and is not used widely [8]. An alternative and commonly used approach is genotyping, where the sequence variants known to define a particular _HLA-B_ allele are detected using PCR primers specific for each variant [8]. Quality assurance studies carried out on the accuracy of _HLA-B*57:01_ testing using sequence-specific primer PCR across multiple laboratories have shown very high sensitivity and specificity, indicating that laboratories using this method appear to be offering effective screening for the allele [35]. Another method that offers cost-effective, rapid, and sensitive screening for _HLA-B*57:01_ or _HLA-B*58:01_ is flow cytometry. _HLA-B*57:01_ and _HLA-B*58:01_ belong to a serological group known as HLA-B17. B17 monoclonal antibodies can be used to identify individuals who carry the HLA-B17 serotype, and these individuals can then undergo

further DNA typing to determine whether they carry the *57:01* or *58:01* risk alleles. As B17 is normally present in less than 10% of the population, assaying for the presence of B17 first allows greater than 90% of a patient population to be eliminated from unnecessary HLA testing [36–38].

It is also possible to test for the presence of an _HLA-B_ allele by genotyping for one or more single nucleotide polymorphisms (SNPs) nearby in linkage disequilibrium with that allele. However, linkage disequilibrium can vary across populations, and this method may have lower accuracy [8,39]. The _HCP5_ SNP rs2395029 has been suggested as a potential marker for abacavir-induced hypersensitivity as the variant allele has shown strong linkage disequilibrium with *57:01* [40–43]. However, it is not in complete concordance with *57:01* [44,45], and individuals with the *57:01* allele, but not the rs2395029 variant allele [44–46] as well as individuals with the rs2395029 variant allele, but not the *57:01* allele [40,41, 44,45] have been noted. This type of incomplete concordance could result in the denial of abacavir to individuals who are not at risk for a hypersensitivity reaction (HSR) or administration of abacavir to individuals who are at risk for an HSR [8,46]. In addition, the studies showing strong linkage between *57:01* and rs2395029 have been carried out in populations of mainly Caucasian or Hispanic descent; the strength of the linkage between the alleles has not been confirmed in large African or Asian populations [8]. Several studies have noted that caution should be exercised when using rs2395029 as a surrogate marker for _HLA-B*57:01_ [8,31,47]. However, because of the inexpensive and straightforward nature of this screening method, some laboratories do choose to perform SNP testing over allele-specific PCR [8].

It is important to note that currently, the high level of polymorphism within the _HLA_ genes makes HLA genotyping at a high resolution challenging [48–50]. The present sequencing methods can result in ambiguous typing results with an inability to resolve phase [48,49]. In addition, different alleles may share similar sequences within the sequenced region [50], and defining polymorphisms may lie outside the amplified region [48,49]. These issues may be resolved through next-generation

sequencing, which allows for clonal amplification and massively parallel sequencing. These two properties provide phase information and the ability to sequence more and larger regions of genes, including intronic regions [48,49].

A list of commercially available genetic tests for various *HLA-B* alleles can be found on PharmGKB at *http://www.pharmgkb.org/views/viewGeneticTests.action*; a more comprehensive list can be found at the Genetic Testing Registry (*http://www.ncbi.nlm.nih.gov/gtr/*). As HLA-B expression is codominant, *HLA-B* genotyping results are either 'positive', with the * allele being present in one or both copies of the gene, or 'negative', where no copies of the allele are present; there is no intermediate phenotype [8].

Important variants
HLA-B*57:01
Abacavir
In addition to being enriched in HIV long-term non-progressors, the *57:01* allele is also associated strongly and independently with the development of an abacavir HSR. Abacavir is a nucleoside reverse transcriptase inhibitor used for the treatment of HIV. It is generally well tolerated, and common side effects include nausea, headache, and diarrhea [51]. However, ~5–8% of patients experience an HSR within the first 6 weeks of treatment [8]. Symptoms of an HSR include at least two of the following: fever, rash, cough, gastrointestinal symptoms (e.g. nausea, vomiting, abdominal pain), dyspnean and fatigue [8]. These symptoms worsen with continued treatment, but typically improve within 24 h after discontinuation. However, drug rechallenge after discontinuation of abacavir because of an HSR can result in symptom recurrence within a matter of hours and potentially life-threatening allergic reactions [52,53]. An overview of abacavir and *57:01* pharmacogenetic studies can be found in Table 2.

In 2002, two separate research groups published the first evidence that *HLA-B*57:01* was present in a significantly higher percentage of patients showing an abacavir HSR compared with patients with no reaction. These studies were carried out in North American [54] and Australian [53] populations, and both included 200 participants. This association was subsequently confirmed by another study within a UK population of 64 patients [55]. However, these three studies were all carried out using predominantly Caucasian men, limiting their scope. Despite this limitation, several clinics began implementing prospective screening of these alleles with success [59–61]. A later study recognized the significance of the allele in White female and Hispanic populations, but found no significant associations for the Black population from this study [62]. This was likely because of the lower number of Black patients in the study and the fact that Black populations tend to have a lower carriage rate of

the allele [56,62] – African populations often have *57:01* allele frequencies of less than 2.5%, in contrast to European populations, who often have *57:01* frequencies of 6–7% [8]. Indeed, a study in Ugandan patients failed to find the *57:01* allele in either patients with an abacavir HSR or tolerant controls [58].

In 2007, a study known as SHAPE (which included a similar number of White and Black participants) found that fewer cases of abacavir HSRs were found among Black patients. However, 100% of both White and Black patients who had immunologically confirmed HSRs were positive for the *HLA-B*57:01* allele [56]. This suggested that although immunologically confirmed HSRs are rare among Black populations because of the reduced frequency of *57:01*, the allele has the same clinical implications in both populations [56]. A definitive association between *57:01* and abacavir HSRs emerged in 2008 with the results of the PREDICT-1 study, a double-blind, prospective, randomized study with 1956 patients from 19 countries. Patients were observed for 6 weeks and divided into two categories: those who underwent screening for the *HLA-B*57:01* allele and were excluded from treatment with abacavir if they tested positive and those who underwent standard care without any screening. Abacavir HSRs were immunologically confirmed with skin patch testing. The results of the study showed that screening eliminated immunologically confirmed HSRs – 0% of the patients screened had an HSR, whereas 2.7% of the control population did. This gave the screening a negative predictive value of 100% [29]. The positive predictive value of *HLA-B*57:01* for abacavir-induced HSRs is typically cited as 55%, implying that around half of all patients who are *HLA-B*57:01* positive will not develop an abacavir HSR [31,63,64]. This indicates that other genes and environmental factors are likely involved in the development of an abacavir-induced HSR. Research in this area has been scarce, but several studies have suggested a member of the 70 kDa heat shock protein (HSP70) family as a potential factor [65–67].

This body of evidence led the Food and Drug Administration (FDA) to implement a boxed warning in 2008, detailing the risk of an HSR for abacavir-treated patients with the *HLA-B*57:01* allele. The FDA also recommended that all patients be screened before being treated, and to not use abacavir in *HLA-B*57:01*-positive individuals [68]. The European Medicines Agency [69], and therapeutic guidelines from the Clinical Pharmacogenetics Implementation Consortium (CPIC) [8] and the Dutch Pharmacogenetics Working Group [70] also recommend genotyping for this allele before beginning abacavir treatment.

The HLA-B protein exerts no direct effect on abacavir pharmacokinetics or pharmacodynamics, and it is still unclear how the *HLA-B*57:01* allele affects susceptibility

Table 2 **Summary of abacavir and *57:01 pharmacogenetic studies**

Population		*57:01 prevalence		P-value	OR (95% CI)	References
American	White (74%), Black (14%), Hispanic (11%), Other (2%)[a]	Case: 37/84 (44%)				Hetherington *et al.* [54]
		Control: 1/113 (0.9%)				
American	White (66%)	Case: 91/189[b] (48%)		8.4 x 10^{-23}	21.4 (9.5 – 48.1)	Hughes *et al.* [55]
		Control: 7/171 (4%)				
	Hispanic (19%)	Case: 11/51[b] (22%)		2.1 x 10^{-4}	30.4 (1.7 – 531)	
		Control: 0/53 (0%)				
	Black (15%)	Case: 3/37[b] (8%)		0.27	3.5 (0.4 – 35.5)	
		Control: 1/41 (2%)				
American	White (54%)	Case: 42/42[c] (100%)			1945 (110 – 34352)	Saag *et al.* [56]
		Control: 8/202 (4%)				
	Black (46%)	Case: 5/5[c] (100%)			900 (38 – 21045)	
		Control: 2/206 (1%)				
Australian	Caucasian (88%), African (3.5%), Indigenous (5.5%), Asian (3%)	Case: 14/18 (78%)		< 0.0001	117 (29 - 481)	Mallal *et al.* [53]
		Control: 4/167 (2%)				
British	Caucasian (94%), Other (6%)[a]	Case: 6/13 (46%)		0.006	7.9 (1.5 – 41.4)	Hughes *et al.* [55]
		Control: 5/51 (10%)				
Canadian	White (66%), Black (16%), Aboriginal (6%), Other (12%)[d]	Case: 18/18 (100%)		<0.0001	6934 (321 – 149035)	Berka *et al.* [57]
		Control: 2/470 (0.4%)				
Ugandan		Case: 0/6 (0%)[e]				Munderi *et al.* [58]
		Control: 0/241 (0%)				

P-values and ORs listed pertain to the risk for an abacavir hypersensitivity reaction (HSR) in patients carrying the *57:01 allele compared with noncarriers. P-values and ORs were calculated by comparing the frequency of *57:01 in patients who developed an HSR compared with the frequency in abacavir-tolerant controls. The prevalence of *57:01 is listed for patients who developed an HSR (case) and in those who were abacavir-tolerant (control). An interactive version of this table is available online at http://www.pharmgkb.org/haplotype/PA165956565, and is updated as new results come to our attention.
CI, confidence interval; HLA, human leukocyte antigen; OR, odds ratio.
[a]Unspecified remaining races.
[b]Data using a 'standard' case definition: cases of hypersensitivity were either 'definite/probable' or 'possible'. Results differed, but were still significant for White and Hispanic patients (and still nonsignificant for Black patients) using a 'restrictive' case definition – only cases that were 'definite/probable'. For 'restrictive' case definition data, please refer to the paper directly.
[c]Immunologically confirmed HSRs. For clinically confirmed HSR data, please refer to the paper directly.
[d]Including 4.7% Indo-Asian, 3.1% Hispanic, 2% Metis and 2.2% oriental or unknown.
[e]Clinically confirmed HSRs.

to drug hypersensitivity. Several hypotheses exist. One is the hapten concept, which suggests that small compounds such as drugs (haptens) bind to the peptides bound to immune receptors such as HLA-B, causing T cells to react and stimulate an immune reaction [71]. Another is the p-i concept (pharmacological interactions with immune receptors), which proposes that drugs bind directly and reversibly to immune receptors, stimulating an immune reaction [71]. Recent evidence seems to support an alternative hypothesis. Two studies, both published in 2012, found that abacavir can bind non-covalently and with specificity to the F pocket of the peptide-binding groove of HLA-B*57:01 [72,73]. Because of the amino acid residues unique to the *57:01 protein, abacavir can bind only to this particular form of HLA-B. The binding of abacavir to HLA-B*57:01 is believed to alter the shape and chemistry of the antigen-binding cleft, and consequently, the repertoire of peptides which can bind the molecule. Indeed, both of these papers, as well as an additional paper by Norcross and colleagues, all identified specific changes in the peptides presented by HLA-B*57:01 in the presence of abacavir compared with HLA-B*57:01 in the absence of the drug [72–74]. As T cells are trained to be tolerant to a particular repertoire of peptides during their development in the thymus, the alteration in the peptides that can be presented may mean that these new peptides are perceived as foreign. This change would stimulate CD8 + T-cell production and response, and would manifest as an abacavir HSR [72,73]. Indeed, CD8 + T cells are abundant in skin biopsies of patients who present with a rash during an abacavir HSR [75].

Flucloxacillin

HLA-B*57:01 is also associated with flucloxacillin drug-induced liver injury (DILI). Flucloxacillin is a semisynthetic penicillin, used widely across Europe and Australia for staphylococcal infection [30,76]. However, it is also associated with the development of cholestatic hepatitis, with risk factors being female sex, age older than 55 years, and treatment duration of longer than 2 weeks [76]. A genome-wide association study found that a marker in complete linkage disequilibrium with HLA-B*57:01 was also strongly associated with flucloxacillin DILI. Further analysis found that patients with this allele had an 80-fold increased risk of developing DILI compared with those without the allele [30]. However, flucloxacillin DILI is a very rare condition, with an estimated prevalence of only 8.5 out of every 100 000 patients. In addition, the positive predictive value of *57:01 for DILI is only 0.12%, meaning that the majority of patients with *57:01 will not develop flucoloxacillin-induced DILI. Indeed, this positive predictive value indicates that almost 14 000 white patients would need to be tested for *57:01 and excluded from receiving the drug to prevent one case of DILI; in non-white or mixed populations, this number could be higher [77]. Given the low positive predictive value and the high number needed to test to prevent one case, pretreatment screening implementation in the clinic is likely not feasible at this time. In their discussion of flucloxacillin HLA-B*57:01 screening, Phillips and Mallal [77] suggest that a more practical approach would be to carefully monitor patients receiving flucloxacillin and to consider their HLA-B*57:01 genotype only if there is biochemical evidence for hepatitis, at which point the drug can be stopped. It is uncertain how the presence of the *57:01 allele leads to an increased risk for flucloxacillin-induced DILI. However, it does not appear to be through the same mechanism as *57:01 and abacavir hypersensitivity: Wuillemin et al. [78] found that in the presence of the HLA-B*57:01 molecule, flucloxacillin stimulated T cells (including CD8 + T cells) according to the p-i concept. In a later study, Wuillemin et al. [79] also showed that DILI might be caused by the infiltration of cytotoxic CD8 + and CD3 + T cells into the liver. Consideration of the results from both studies of Wuillemin and colleagues provides a possible explanation for the connection between *57:01 and DILI.

HLA-B*58:01
Allopurinol

The HLA-B*58:01 allele is associated strongly with allopurinol-induced SCARs, which include hypersensitivity syndrome (HSS) and SJS/TEN [80]. Allopurinol is mainly used for conditions associated with hyperuricemia, such as gout and tumor lysis syndrome [81]. The drug works by inhibiting the enzyme xanthine oxidase, which is responsible for the conversion of hypoxanthine and xanthine into uric acid. In this manner, the drug lowers the amount of uric acid created in the body [80, 82]. Most side effects from allopurinol are mild, with the most common complaint being gastrointestinal upset [80, 82]. However, allopurinol has also been associated with severe adverse reactions. SJS and TEN (or SJS/TEN when referencing both) are two forms of the same condition. Both involve severe mucocutaneous blistering and epidermal detachment, and usually present 1–3 weeks after treatment begins. SJS and TEN are distinguished by the amount of skin detachment: SJS is classified as 1–10% detachment of body surface area (BSA), SJS and TEN overlap as 10–30% of BSA, and TEN as greater than 30% of BSA. Although the occurrence of these symptoms is rare (only two patients per million per year), SJS and TEN can be permanently disabling or even fatal. The mortality rate correlates with the level of skin detachment, ranging from a 1–5% mortality rate for SJS to a 25–35% mortality rate for TEN [83,84]. In contrast to SJS/TEN, HSS (also known as drug-induced hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms) typically has organ involvement, such as hepatitis or nephritis, in addition to fever and a severe rash [85–87]. The risk of developing SCARs during allopurinol treatment is 0.1–0.4% [80]. In some

association studies with allopurinol-induced SCARs, only the relationship with SJS/TEN is discussed and HSS is not used as an associated phenotype.

The first association between *HLA-B*58:01* and SCARs emerged from a 2005 Taiwanese study on Han Chinese patients, which found that 100% of the 51 patients who developed allopurinol-induced SCARs had the *HLA-B*58:01* allele, whereas only 15% of the 135 allopurinol-tolerant patients carried the allele. This yielded an odds ratio of 580 for the development of SCARs with this particular allele [85]. Follow-up studies in Thai, Korean, Japanese, Han Chinese, and European populations also found significant results [32,88–95]. However, differences exist between these ethnicities when considering the magnitude of risk for developing SCARs. Although Han Chinese and Thai patients show exceptionally high odds ratios for developing SCARs, European and Japanese *58:01* carriers show comparatively much lower risks for the development of SCAR (Table 3). This disparity in odds ratios is likely because of variations in *58:01* frequencies between ethnicities, rather than a differing effect of the *58:01* allele depending on ethnicity. Although the Han Chinese and Thais tend to have *58:01* allele frequencies of around 8%, Europeans and Japanese have allele frequencies of ~1.4 and 0.5%, respectively [6,32,92,94]. The *58:01* allele may also be associated with a more mild cutaneous adverse drug reaction, maculopapular eruption (MPE), which presents as a rash consisting of macules and papules. Cao et al. [88] found that 100% of their Han Chinese patients who developed an MPE while receiving allopurinol carried the *58:01* allele. In contrast, Lee and colleagues found that none of their 12 patients who presented with MPE carried the *58:01* allele, whereas six out of 11 of their patients who developed SCARs did. However, this may be because of the large presence of Caucasians in their study, a population with a low *58:01* frequency. Eleven of the patients with MPE were Caucasian, as were the five patients who developed SCARs, but did not carry *58:01* [96]. Table 3 presents an overview of allopurinol and *58:01* pharmacogenetic studies, and indicates whether a study has analyzed SCARs, SJS/TEN, HSS, or MPE.

Because of the strong associations observed between *58:01* and allopurinol, the CPIC recommends genotyping before treatment with allopurinol and suggests that the drug should be contraindicated in patients with one or more *58:01* alleles [80]. The American College of Rheumatology also recommends that *58:01* screening be considered when assessing the risks of the drug, especially in populations with high frequencies of the allele, such as the Han Chinese or Thais [101]. Unlike abacavir, no clinical trials have been published that test whether genotyping for the presence of *HLA-B*58:01* can reduce the number of SCAR or SJS/TEN cases in patients treated with allopurinol. On the basis of data from Han

Chinese and Thai populations, the negative predictive value of this allele for SJS/TEN development is 100%, but the positive predictive value is only about 1.5% [80]. This indicates that most patients who carry the allele will not develop SJS/TEN. Discovery of new genetic, or nongenetic, factors that lead to SJS/TEN or SCAR development may help increase the positive predictive value. Studies on the mechanism of SCAR development in *HLA-B*58:01* carriers have been limited. A recent study suggested that it is a metabolite of allopurinol, oxypurinol, which causes the HSR in individuals with the *HLA-B*58:01* allele: oxypurinol was found to bind to the F pocket of HLA-B*58:01 through the p-i mechanism with a higher affinity compared with allopurinol [102].

HLA-B*15:02
Carbamazepine

*HLA-B*15:02* is associated strongly with SJS/TEN in patients taking CBZ, an anticonvulsant and mood-stabilizing drug. Along with epilepsy and bipolar disorder, CBZ is also used to treat a variety of other conditions, such as schizophrenia, trigeminal neuralgia, and carpal tunnel syndrome [103]. As with *58:01*, the allele frequency of *15:02* varies worldwide. Han Chinese have an average allele frequency of almost 6%, but this value can range anywhere from 1.9 to 12.4% depending on the population [6]. In addition, other Chinese populations, such as the Bulang, can have an allele frequency of close to 36% [104]. Thai and Malaysian populations also have high *15:02* allele frequencies, with average allele frequencies of close to 8%. In contrast, Koreans show a frequency of 0.3%, Japanese a frequency of 0.1%, and Caucasians a frequency of only 0.06% [6]. These percentages correlate with the number and strength of studies finding significant results linking *15:02* with the development of SJS/TEN: studies in Caucasian [105–107] and Japanese [93] patients have been limited and have shown exclusively nonsignificant results. One study in Koreans found a significant association when comparing allele frequencies for SJS/TEN patients against population controls, but no significant association when comparing against CBZ-tolerant controls [108]. In contrast, studies in Han Chinese are numerous and show very high odds ratios for CBZ-induced SJS/TEN [107, 109–114]. Studies in Indian [115], Thai [34,116,117], Malaysian [118,119], and Singaporean [120,121] populations have also found significant associations. These pharmacogenetic studies are summarized in Table 4. In addition, three meta-analyses (not included in Table 4) that combined studies with Chinese, Korean, Malaysian, and Thai patients all found odds ratios of ~80 for the development of CBZ-induced SJS/TEN in patients carrying the *15:02* allele [126–128].

Because of the low frequency in Korean, Japanese, and Caucasian populations, screening for exclusively *15:02* may not be sufficient from a global perspective. Other

Table 3 **Summary of allopurinol and *58:01* pharmacogenetic studies**

Population	*58:01* prevalence	P-value	Odds ratio (95% CI)	References
Australian	Case (SCARs)[a]: 6/11 (55%)			Lee et al. [96]
	Case (MPE)[b]: 0/12 (0%)			
European	Case (SJS/TEN; Caucasians only): 15/27 (55%)			Lonjou et al. [94]
	Case (SJS/TEN; Mixed ethnicities)[c]: 19/31 (61%)			
	Population control[d]: 28/1822 (1.5%)			
	vs Caucasians only	$<1 \times 10^{-6}$	80 (34 – 187)	
	vs Mixed ethnicities	$<1 \times 10^{-8}$	61 (32 – 118)	
European	Case (SCARs)[e]: 16/25 (64%)			Goncalo et al. [90]
	Tolerant control[f]: 1/23 (4.3%)	5.9×10^{-4}	39.1 (4.5 – 340)	
	Population control[f]: 63/3200 (2%)		88.5 (38 – 208)	
Han Chinese	Case (SCARs): 51/51 (100%)			Hung et al. [85]
	Tolerant control: 20/135 (15%)	4.7×10^{-24}	580 (34 – 9781)	
	Population control: 19/93 (20%)	8.1×10^{-18}	393 (23 – 6625)	
Han Chinese	Case (SCARs): 19/19 (100%)		230 (11.7 – 4520)	Chiu et al. [89]
	Tolerant control: 4/30 (13%)			
Han Chinese	Case (SCARs): 16/16 (100%)			Cao et al. [88]
	Case (MPE): 22/22 (100%)			
	Case (All cADRs[g]): 38/38 (100%)			
	Tolerant control: 7/63 (11%)			
	vs SCAR cases	7.4×10^{-12}	248 (13.5 – 4585)	
	vs MPE cases	9.2×10^{-14}	339 (18.6 – 6186)	
	vs cADR cases	7.0×10^{-18}	580 (32.1 – 10457)	
	Population control: 80/572 (14%)			
	vs SCAR cases	1.8×10^{-18}	202 (12 – 3398)	

Table 3   (*continued*)

	vs MPE cases	3.7×10^{-24}	275 (16.5 – 4584)	
	vs cADR cases	3.2×10^{-38}	471 (28.7 – 7744)	
Han Chinese	Case (HSS): 1/1 (100%)			Huang *et al.* [97]
Han Chinese	Case (SJS): 1/1 (100%)			Lee *et al.* [98]
	Tolerant control: 0/1 (0%)			
Japanese	Case (SJS/TEN): 4/20[h] (20%)	<0.0001	40.8 (10.5 – 159)	Kaniwa *et al.* [93]
	Population control: 6/986[h] (0.6%)			
Japanese	Case (SJS/TEN): 10/36[h] (28%)	5.4×10^{-12}	62.8 (21.2 – 186)	Tohkin *et al.* [95]
	Population control: 6/986[h] (0.6%)			
Japanese	Case (SCARs): 3/3 (100%)			Dainichi *et al.* [99]
Kenyan	Case (TEN)[i]: 1/1			Kemen *et al.* [100]
Korean	Case (SCARs): 24/26 (92%)			Kang *et al.* [92]
	Tolerant control: 6/57 (11%)	2.5×10^{-11}	97.8 (18.3 – 522)	
	Population control: 59/485 (12%)	2.5×10^{-16}	83.0 (19.0 – 361)	
Korean	Case (SCARs): 9/9 (100%)			Jung *et al.* [91]
	Tolerant control: 41/432 (9.5%)	<0.001	179 (10.2 – 3152)	
	Population control: 59/485 (12%)	<0.001	136 (7.8 – 2381)	
Thai	Case (SJS/TEN): 27/27 (100%)	1.6×10^{-13}	348 (19.2 – 6337)	Tassaneeyakul *et al.* [32]
	Tolerant control: 7/54 (13%)			

P-values and odds ratios (ORs) listed pertain to the risk for allopurinol-induced adverse reactions in patients carrying the *58:01 allele compared with noncarriers. *P*-values and ORs were calculated by comparing the frequency of *58:01 in patients who developed adverse reactions to the frequency of *58:01 in allopurinol-tolerant controls or in healthy population controls. The prevalence of *58:01 is listed for patients who developed adverse reactions (case) and in those who were allopurinol-tolerant (tolerant control) or from a healthy population (population control). An interactive version of this table is available online at *http://www.pharmgkb.org/haplotype/PA165956630*, and is updated as new results come to our attention.

cADRs, cutaneous adverse drug reactions; CI, confidence interval; HSS, hypersensitivity syndrome; MPE, maculopapular eruption; SCARs, severe cutaneous adverse drug reactions; SJS/TEN, Stevens–Johnson Syndrome/toxic epidermal necrolysis.

[a]Four of the six patients with *58:01 were of Southeast Asian origin and two were Caucasian. All patients with SCARs but without *58:01 (i.e. the five remaining patients) were Caucasian.

[b]One patient was of Southeast Asian origin and the remaining patients were Caucasian.

[c]Includes 27 Caucasian patients, and four non-Caucasian patients of Pakistani, Cuban, Indian, and Senegalese background; all four non-Caucasian patients carried the *58:01 allele.

[d]Controls were from Western Europe, but specific ethnic information was not provided; the majority of these controls were assumed to be Caucasian.

[e]Cases were exclusively Caucasian.

[f]Ethnicity of the controls was not specified.

[g]MPE and SCAR.

[h]Allele frequencies.

[i]Born in Germany to Kenyan parents.

Table 4   Summary of carbamazepine and *15:02 pharmacogenetic studies

Population	*15:02 prevalence	P-value	Odds ratio (95% CI)	References
British[a]	Case: 0/2 (0%)			Alfirevic et al. [105]
	Tolerant control: 0/43 (0%)			
Canadian[b]	Case: 3/9 (33%)[c]	0.002	38.7 (2.7 – 2240)	Amstutz et al. [106]
	Tolerant control: 1/87 (1%)[d]			
European	Case: 4/12 (33%)[e]			Lonjou et al. [122]
European	Cases: 0/20 (0%)			Genin et al. [107]
	Tolerant control: 0/43 (0%)	NS		
	Population control: 4/8862 (0.1%)	NS		
Han Chinese	Case: 9/9 (100%)			Wang et al. [113]
	Tolerant control: 11/80 (13.8%)	<0.001	115 (6.3 – 2111)	
	Population control: 11/62 (17.7%)	<0.001	85.1 (4.6 – 1570)	
Han Chinese	Case: 16/17 (94%)			Zhang et al. [114]
	Tolerant control: 2/21 (9.5%)	<0.0001	152 (12 – 1835)	
	Population control: 17/185 (9.2%)	<0.0001	158 (19 – 1266)	
Han Chinese	Case: 44/44 (100%)			Chung et al. [109]
	Tolerant control: 3/101 (3%)	3.1×10^{-27}	2504 (126 – 49522)	
	Population control: 8/93 (8.6%)	1.4×10^{-21}	895 (50 – 15869)	
Han Chinese	Case: 59/60 (98.3%)	1.6×10^{-41}	1357 (193 – 8838)	Hung et al. [123]
	Tolerant control: 6/144 (4.2%)			
Han Chinese	Case: 13/18 (72.2%)			Shi et al. [112]
	Tolerant control: 12/93 (12.9%)	<0.001	17.6 (5.3 – 58.1)	
	Population control: 10/93 (10.8%)	<0.001	21.6 (6.4 – 73.3)	
Han Chinese	Case: 24/26 (92.3%)	3.5×10^{-18}	89.3 (19 – 414)	Cheung et al. [124]
	Tolerant control: 16/135 (11.9%)			
Han Chinese	Case: 8/8 (100%)			Wu et al. [125]
	Tolerant control: 4/50 (8%)		184 (33.2 – 1021)	
	Population control: 6/71 (8.5%)		173 (36 – 835)	

Table 4 (*continued*)

Han Chinese	Case: 99/112 (88%)	5.8×10^{-43}	97.6 (42 – 227)	Hsaio *et al.* [111]
	Tolerant control: 11/152 (7%)			
Han Chinese	Case: 8/35 (22.9%)	0.000	18.2 (3.7 – 90.7)	He *et al.* [110]
	Tolerant control: 2/125 (1.6%)			
Han Chinese	Case: 41/53 (77.4%)			Genin *et al.* [107]
	Tolerant control: 4/72 (5.6%)	< 0.001	58.1 (17.6 – 192)	
	Population control: 60/710 (8.5%)	< 0.001	37.0 (18.5 – 74.2)	
Indian	Case (SJS only): 6/8 (75%)	0.0014	71.4 (3.0 – 1698)	Mehta *et al.* [115]
	Tolerant control: 0/10 (0%)			
Japanese	Case: 0/7 (0%)			Kaniwa *et al.* [93]
Korean	Case: 1/7 (14.3%)			Kim *et al.* [108]
	Tolerant control: 2/50 (4%)	NS	23.3 (0.9 – 634)	
	Population control: 2/485 (0.4%)	0.042	40.3 (3.2 – 506)	
Malaysian	Case: 12/16 (75%)	7.9×10^{-6}	16.2 (4.6 – 62.4)	Chang *et al.* [118]
	Population control: 47/300 (15.7%)			
Malaysian	Case (SJS only): 6/6 (100%)[f]	0.0003		Then *et al.* [119]
	Tolerant control: 0/8 (0%)[g]			
Singaporean	Case: 5/5 (100%)[h]		27.2 (2.7 – ∞)	Chong *et al.* [120]
	Tolerant control: 1/10 (10%)[i]			
Singaporean	Case: 13/13 (100%)[j]	6.9×10^{-8}	181 (8.7 – 3785)	Toh *et al.* [121]
	Tolerant control: 3/26 (11.5%)[k]			
Thai	Case (SJS only): 6/6 (100%)	0.0005	25.5 (2.7 – 243)	Locharenkul *et al.* [117]
	Tolerant control: 8/42 (19%)			
Thai	Case: 37/42 (88%)	2.9×10^{-12}	54.8 (14.6 – 205)	Tassaneeyakul *et al.* [34]
	Tolerant control: 5/42 (12%)			
Thai	Case: 32/34 (94.1%)	<0.001	75.4 (13.0 – 719)	Kulkantrakom *et al.* [116]
	Tolerant control: 7/40 (17.5%)			

P-values and odds ratios (ORs) listed pertain to the risk for carbamazepine-induced Stevens–Johnson syndrome or toxic epidermal necrolysis (SJS/TEN) in patients carrying the *15:02 allele compared with noncarriers. *P*-values and ORs were calculated by comparing the frequency of *15:02 in patients who developed SJS/TEN to the frequency in carbamazepine-tolerant controls or in healthy population controls. The prevalence of *15:02 is listed for patients who developed SJS/TEN (case) and in those who were carbamazepine-tolerant (tolerant control) or from a healthy population (population control). An interactive version of this table is available online at *http://www.pharmgkb.org/haplotype/PA165954769*, and is updated as new results come to our attention.

CI, confidence interval; NS, nonsignificant; SJS, Stevens–Johnson syndrome.

[a]Caucasian only.
[b]Pediatrics. Multiple ethnicities included, please refer to the paper directly for more information.
[c]All three case patients with the allele were of Asian ancestry, countries unspecified.
[d]The one tolerant control with the allele was of Asian ancestry, country unspecified.
[e]Four patients with *15:02 were of Asian ancestry (Vietnam, China, Cambodia, and Reunion Island). The remaining eight patients without *15:02 were Caucasian (Germany, France).
[f]Four Malaysian, two Chinese.
[g]Six Malaysian, two Chinese.
[h]Pediatrics. Two Chinese, three Malaysian.
[i]Pediatrics. Seven Chinese, two Malaysian, one Indian.
[j]Ten Chinese, three Malaysian.
[k]Twenty Chinese, six Malaysian.

alleles have shown significant relationships with SJS/TEN within these ethnicities, such as *HLA-B*07:02* [105] and *HLA-A*31:01* [107,129–131]. Several studies in Japanese, Korean, and Han Chinese patients suggest that carriers of the *HLA-B*15:11* alleles [108,112,132] have an increased risk of developing SCARs. The average allele frequencies for *15:11* in Japanese and Korean populations are higher than for *15:02*, with values of 0.4–0.8% for the Japanese and 1.6% for Koreans [6]. Both *15:02* and *15:11* are part of the same HLA-B75 serotype [108,132], and the two alleles share a 98.6% amino acid sequence homology [112]. Therefore, they may share similar structures that lead to the triggering of an immune reaction when CBZ is administered [112]. Studies on *07:02*, *31:01*, and *15:11* are limited compared with those on *15:02*, and research into alleles beyond *15:02* may help improve predictive genetic testing for SJS/TEN.

Unlike other *HLA-B* alleles, the associations between *HLA-B*15:02* and CBZ are phenotype specific. Many of the studies mentioned above ([105–107,111,113,117,119, 120,123,125,126]) also looked for associations with HSS, as well as MPE. However, none of the studies found any associations between *15:02* and CBZ-induced HSS or MPE, indicating that the allele may be particular to the development of SJS or TEN. One study has assessed the link between *15:11* and CBZ-induced HSS, and found no significant association [108]. In contrast, *HLA-A*31:01* has shown strong associations with the development of CBZ-induced HSS or MPE in European [106,107,130], Han Chinese [107,123], Japanese [131], and Korean [108] populations, as well as in a meta-analysis that included patients of all four aforementioned ethnicities [126].

A 2011 study assessed the value of genotyping before CBZ treatment, with close to 4500 Taiwanese individuals of Han Chinese descent participating. The 367 patients who were found to be positive for *15:02* were told not to take the medication, whereas the remaining 4120 took the drug as normal. Because of ethical considerations, historical incidences of SJS/TEN were used as a control. Although no cases of SJS/TEN occurred in the study, historical data estimations found that 10 cases of SJS/TEN would have likely appeared in the study cohort, a significant difference [133]. Although those of Caucasian ethnicity do tend to have lower frequencies of the *15:02* allele, genotyping before treatment is still useful for these individuals as they may be unaware of Asian ancestry or fail to alert their doctor to their heritage. At this time, the US FDA recommends genotyping for *15:02* before treatment with CBZ in all Asian populations, although it does not make recommendations for patients of other ethnicities [134]. The negative predictive value of this allele for patients in Taiwan is suggested to be 100% and the positive predictive value is suggested to be 7.7% [134]. This low positive predictive value implies that additional genetic or nongenetic factors likely play a role in the development of SJS/TEN in patients taking CBZ. Despite the low positive predictive value, it may be advisable to avoid the drug in *15:02*-positive patients, given that there are effective alternatives to CBZ [129,134]. Indeed, both CPIC and the Canadian Pharmacogenomics Network for Drug Safety recommend that a different agent be used if a patient is found to be a carrier of the *15:02* allele because of a strong increased risk for SJS/TEN [39,129].

The mechanism of CBZ-induced SJS/TEN is still unclear. In a recent study, Wei and colleagues found that peptide-loaded HLA-B*15:02 presented CBZ to cytotoxic T lymphocytes without any previous processing or drug metabolism. Only HLA-B*15:02 could bind CBZ, as opposed to HLA-B*15:01, *15:03, *40:01, or *51:01. Endogenous peptides already loaded onto the molecule were found to be required before CBZ could be presented [135]. The authors suggested that the binding of CBZ to HLA-B*15:02 activates and induces clonal expansion of cytotoxic (CD8 +) T lymphocytes, eliciting a severe immune reaction that leads to SJS or TEN [135]. The skin reaction observed in cases of SJS or TEN are believed to be because of CD8 + T lymphocytes, which are found in abundance in skin blister cells of patients with SJS/TEN, and are believed to release cytotoxic proteins that induce keratinocyte apoptosis [135–137]. One of the studies that looked at the mechanism of abacavir-induced HSR also found that CBZ binds to HLA-B*15:02, but no mention was made on whether loaded endogenous peptides are necessary. However, the authors noted that there was a repertoire shift in the peptides bound to HLA-B*15:02 in the presence of CBZ, albeit at a smaller magnitude than that of peptides bound to *57:01 in the presence of abacavir. This change could lead to an immune reaction by the same mechanism suggested for an abacavir-induced HSR [72]. Further studies in this area should help elucidate the precise manner in which the *15:02* allele affects the development of SJS/TEN in patients taking CBZ.

Phenytoin and other antiepileptics
15:02 is also associated with SJS/TEN in patients taking phenytoin, another antiepileptic; pharmacogenetic results are presented in Table 5. Studies linking *15:02* with SJS/TEN include four in Han Chinese patients [124,138 –140] and one in Thai patients limited only to SJS cases [117]. In addition, a meta-analysis of four studies found a significant association between *15:02* and phenytoin-induced SJS/TEN [128]. Although these studies have shown statistically strong results, they have been limited in number and population size. One study in Thai children found no link between *15:02* and phenytoin-induced SCARs [141]. Variations within the *CYP2C9* gene have also shown associations with phenytoin-related

Table 5 Summary of phenytoin and *15:02 pharmacogenetic studies

Population	*15:02 prevalence	P-value	Odds ratio (95% CI)	References
Han Chinese	Case (SJS/TEN): 7/15 (46.7%)	0.045	3.5 (1.1 – 11.2)	Chung *et al.* [124]
	Tolerant control: 15/75 (20%)			
Han Chinese	Case (SJS/TEN): 8/26 (30.8%)	0.0041	5.1 (1.8 – 15.1)	Hung *et al,* [138]
	Tolerant controls: 9/113 (8%)			
Han Chinese	Case (SJS): 1/2 (50%)	0.0012[b]	6.1 (2.2 – 17.0)	Min *et al.* [139]
	Combined case (SJS/TEN)[a]: 10/29 (35%)			
	Tolerant control: 9/113 (8%)			
Han Chinese	Case (SJS/TEN): 13/48 (27.1%)	0.0253[c]	5.0 (2.0 – 13)	Chung *et al.* [140]
	Tolerant control: 9/130 (6.9%)			
Thai	Case (SJS): 4/4 (100%)	0.005	18.5 (1.8 – 188)	Locharernkul *et al.* [117]
	Tolerant controls: 0/7 (0%)			
Thai	Case (SCARs): 1/17 (5.88%)	0.35	0.35 (0.03 – 3.9)	Manuyakorn *et al.* [141]
	Tolerant control: 3/17 (17.6%)			

P-values and odds ratios (ORs) listed pertain to the risk for phenytoin-induced Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) in patients carrying the *15:02 allele compared with noncarriers. P-values and ORs were calculated by comparing the frequency of *15:02 for patients who developed SJS/TEN to the frequency in phenytoin-tolerant controls. The prevalence of *15:02 is listed in patients who developed SJS/TEN (case) and in those who were phenytoin-tolerant (tolerant control). An interactive version of this table is available online at *http://www.pharmgkb.org/haplotype/PA165954769*, and is updated as new results come to our attention. CI, confidence interval; SCARs, severe cutaneous adverse drug reactions.
[a]Combined study results from Tassaneeyakul and colleagues [34,94,124].
[b]P-value for comparison in *15:02 frequencies between tolerant controls and combined cases.
[c]Bonferroni-corrected P-value.

adverse reactions. Phenytoin is primarily metabolized to its inactive form by CYP2C9, and alleles that result in decreased enzymatic activity, specifically *CYP2C9*2* and *3*, have been linked with increased phenytoin concentrations [142–145] and an increased risk for neurological toxicities [146,147] and cutaneous adverse drug reactions [140,148]. Consideration of both *HLA-B*15:02* and *CYP2C9*2* and *3* may be important in any future clinical pretreatment screening programs.

Currently, the FDA recommends that physicians consider the risks associated with SJS/TEN in patients taking phenytoin who have Asian ancestry and carry the *15:02 allele, particularly in light of the evidence linking *15:02 with CBZ-induced SJS/TEN [149]. Phenytoin, CBZ, oxcarbazepine, phenobarbital, and lamotrigine are all known as aromatic antiepileptic drugs (AEDs) because of the presence of an aromatic ring in their structure – symptoms of hypersensitivity were found to occur twice as often in patients administered aromatic AEDs as

opposed to nonaromatic AEDs (e.g. levetiracetam or topiramate) [150], suggesting that the presence of the ring may be involved in the higher risk for adverse reactions [151]. A recent study looking at children taking CBZ, oxcarbazepine, or phenobarbital found that those who developed SJS had a higher frequency of the *15:02 allele compared with tolerant controls or healthy population controls [152]. Wei *et al.* [135], in their study on the mechanism by which *15:02 is associated with CBZ-induced SJS/TEN, noted that oxcarbazepine, which has a tricyclic ring structure similar to CBZ, was also capable of binding with *HLA-B*15:02*, although not as strongly as CBZ. However, studies linking *HLA-B*15:02* with oxcarbazepine-induced SJS or MPE have shown mixed results [138,153–155]. Although no individual studies have found significant associations between *15:02 and lamotrigine-induced adverse reactions [124, 138,156,157], a meta-analysis of four studies did find a significantly increased risk for SJS/TEN for patients carrying *15:02 who receive lamotrigine [128].

Conclusion

The *HLA-B* gene has shown associations with a wide range of diseases and adverse drug reactions. Despite this, very little is understood about the mechanisms by which variations in an immune system gene can affect the propensity for certain pharmacological reactions or particular illnesses. However, some progress has been made in understanding the mechanisms behind abacavir HSRs and CBZ-induced SJS/TEN, particularly in the last couple years. Studies on abacavir HSRs have paved the way for pharmacogenetic implementation within the clinic: *HLA-B*57:01* genotyping before abacavir treatment is one of the key examples of pharmacogenetics being used in routine medical practice. Given that *HLA-B*58:01* and *15:02* have also shown strong pharmacogenetic associations, these alleles may also be good candidates for clinical integration. *HLA-B* has been shown to be an influential gene across many areas of medicine, and future studies should improve our understanding of its role in both disease and pharmacology.

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Conflicts of interest

R.B.A. and T.E.K. are stockholders in Personalis Inc. For the remaining authors there are no conflicts of interest.

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