**Pharmacogenomics of Drug Hypersensitivity: Technology and Translation**

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## Keywords

Drug hypersensitivity; HLA; pharmacogenetics; implementation.

**Key points**

* Drug hypersensitivity reactions are uncommon and genetically-mediated adverse effects, that contribute significantly to drug-related morbidity and mortality.
* Genetic variability in different HLA loci has been associated with different types of hypersensitivity reactions to a number of drugs, and the importance of particular HLA alleles has been validated by functional studies.
* Implementation of genetic testing as a precision medicine approach to prevent drug hypersensitivity reactions has been slow and challenging and further work is essential to maximize the impact of pharmacogenomic discoveries to improve translation to the clinic and outcomes.

**Synopsis (98 words)**

Hypersensitivity reactions are caused by many structurally unrelated drugs used for many different diseases. These reactions vary in severity and can be fatal. Only a minority of patients are affected by drug hypersensitivity reactions. Predisposition seems to be mediated by genetic factors, particularly within the HLA system. Apart from *HLA-B\*57:01* testing which is routine to prevent abacavir hypersensitivity, uptake of HLA testing into clinical practice has been slow and challenging. As genomic medicine becomes mainstreamed, it will be important for genetic testing in this area to move from the current reactive strategy to a more pre-emptive approach.

## Introduction

Pharmacogenomics aims to understand how genetic variation influences drug response. This understanding has the potential to support clinicians to deliver personalized therapy and to reduce the incidence of adverse drug reactions, including drug hypersensitivity reactions1.

Drug hypersensitivity reactions are an inappropriate response leading to tissue damage from an otherwise non-toxic agent2. They can affect multiple organs in isolation or in combination including the liver, skin, bone marrow and muscle3 (figure 1). They vary in severity and can sometimes cause death. They usually affect a small percentage of the population and although they can be dose dependent, unlike predictable pharmacological adverse drug reactions, they do not show a typical dose-response relationship. Pharmacogenomic studies have shown associations between several HLA markers and hypersensitivity to a wide range of drugs3. As pharmacogenomics becomes part of mainstream medicine, it is important that researchers start to develop strategies, and the evidence base, to implement these HLA associations into clinical practice.

**HLA and Immunogenomic Contributors to Drug Hypersensitivity**

The HLA system is the human form of the vertebrate major histocompatibility complex (MHC). It plays a crucial role in allowing the immune system to discriminate between self and non-self. HLA proteins contain peptide-binding grooves which collectively present a repertoire of thousands of different peptides to T cells. Self-derived peptides are ignored due to exposure during thymic development and foreign peptides are recognized by the T cells, initiating an immune response under the control of regulatory pathways. The HLA locus, located on the short arm of chromosome 6, is highly polygenic, with HLA molecules classified according to function. Class I HLA molecules, HLA-A, -B and -C, are found on the surface of all nucleated cells and present intracellularly derived peptides to CD8+-T cells. Class II HLA molecules, HLA-DRA, -DRB1, -DRB3, -DRB4, -DRB5, -DQA1, -DQB1, -DPA1 and -DPB1, are located on the surface of antigen presenting cells and present a variety of extracellularly derived peptides to CD4+ T cells. The HLA class I loci and in particular HLA-B, are highly polymorphic giving rise to numerous variant HLA alleles; the IPD-IMGT/HLA Database currently reports 7354, 8456 and 7307 HLA-A, -B and -C alleles respectively4. The HLA peptide-binding grooves show the highest sequence variation, maximising the range of different peptides that can bind. The prevalence of specific HLA alleles can vary widely between ethnic groups, and as a result the incidence of some HLA associated hypersensitivity reactions also varies between groups.

The HLA system is essential for our response to disease. However, the same HLA alleles can predispose certain individuals to drug hypersensitivity reactions. In such reactions, the drug or drug metabolite(s) interfere with the natural HLA-T-cell interaction leading to T-cell activation and an aberrant immune response5. Drug molecules are proposed to act on HLA molecules and activate T cells through three different mechanisms. In the hapten model, the drug forms a covalent bond with a protein which is then processed, bound by an HLA molecule and presented to the T-Cells. In the p-i model, the drug forms non-covalent interactions resulting in the formation of a complex comprising the drug, a peptide, HLA protein and T-cell receptor. This complex seems to be stable enough to trigger an immune response. In the altered peptide repertoire model, the drug molecule forms a non-covalent interaction with the peptide binding groove of the HLA molecule, altering the repertoire of bound peptides. It is important to note that these mechanisms are not mutually exclusive and there is good evidence for each of them occurring for different drugs, and sometimes for the same drug5.

Research over the last two decades has highlighted some important aspects of the associations between drugs, their propensity to cause hypersensitivity reactions, and specific HLA alleles, which are outlined in **box 1**. **Box 2** also provides some examples of other factors which may modulate the incidence of hypersensitivity, over and above the presence of risk HLA alleles.

**Examples of HLA Associations**

It is not the purpose of this article to provide a comprehensive overview of the many associations that have been reported with different drug-induced hypersensitivity reactions. Readers are referred to recent reviews5,20,21. Here we provide a description of some key examples.

***Cutaneous adverse reactions***

The skin is the organ most commonly affected in hypersensitivity reactions, either in isolation or as part of multi-system adverse reactions. The phenotypes vary greatly, from mild maculopapular exanthema to serious, often fatal reactions, such as toxic epidermal necrolysis.

Abacavir hypersensitivity is the poster child of HLA pharmacogenomics. The initial description of the association of abacavir hypersensitivity9 with *HLA-B\*57:01* in 2002 has subsequently been replicated many times in different ethnic groups (table 1). The utility of pre-prescription genotyping was shown in the PREDICT-1 trial22. Determination of whether a patient is positive for *HLA-B\*57:01* prior to prescribing abacavir is considered to be routine clinical practice in the developed world. Since 2008 it has been mandated in drug labels and in guidelines and has reduced the incidence of abacavir hypersensitivity23.

Carbamazepine hypersensitivity manifests in many different ways. Skin manifestations can vary in severity, and may be accompanied by internal organ involvement, in particular the liver. However, the liver can also be affected in isolation. In South-East Asian populations, a strong association has been shown between *HLA-B\*15:02* and carbamazepine-induced Stevens-Johnson Syndrome and toxic epidermal necrolysis (SJS/TEN)35. Carbamazepine-induced SJS/TEN can also be caused by the most common B75 serotype alleles in Southeast Asia36, *HLA-B\*15:08, HLA-B\*15:11*, and *HLA-B\*15:21.*  By contrast, in European ancestry populations, *HLA-A\*31:01* has been associated with various carbamazepine hypersensitivity phenotypes, ranging from maculopapular exanthem to SJS/TEN37, and more recently with liver injury7. These associations have been replicated in many different ethnic groups (table 2). While *HLA-B\*15:02* genotyping is recommended in many regulatory labels, *HLA-A\*31:01* is only mentioned for information. However, a Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline suggests that genotyping for both alleles prior to carbamazepine prescription be considered36.

Allopurinol, a drug used for the treatment of gout, can cause serious cutaneous adverse reactions, including ‘drug reaction with eosinophilia and systemic symptoms’ (DRESS) and SJS/TEN. Work from Taiwan showed a strong association between these hypersensitivity reactions and *HLA-B\*58:01*77; this has now been replicated in many studies worldwide, but in particular in SE Asian populations, where the frequency of *HLA-B\*58:01* is higher than in European Ancestry populations (table 3). *HLA-B\*58:01* has also recently been shown to be associated with allopurinol hepatotoxicity where some of the cases also had manifest allopurinol DRESS78. Pre-prescription genotyping has shown to be cost-effective in some Asian countries 79. In European and African populations, HLA-B\*58:01 explains approximately 60% of allopurinol associated DRESS and SJS/TEN.

Other important hypersensitivity reactions with predominantly cutaneous manifestations which have been reported recently include *HLA-B\*13:01* and dapsone hypersensitivity96*, HLA-A\*32:01* and vancomycin DRESS97 and *HLA-DRB1\*10:01* and beta-lactam induced immediate hypersensitivity reactions98.

**Hepatic adverse reactions**

Many different HLA and non-HLA alleles have been associated with drug-induced liver injury (DILI) caused by a variety of therapeutic substances – readers are referred to more comprehensive reviews of this subject21,99. Perhaps the most striking example is that of flucloxacillin-induced hepatic injury and its association with *HLA-B\*57:01*. This was first described by Daly et al10 in 2009 – a GWAS in 51 cases of flucloxacillin DILI showed a very strong association (P=10-33) with rs2395029, which was in linkage disequilibrium with *HLA-B\*57:01*. Functional immunological analysis showed the presence of drug-specific CD8+ HLA-restricted T-cell clones in patients with liver injury, with T-cell activation being processing-dependent100. A more recent evaluation of a larger number of patients has shown that *HLA-B\*57:03* also predisposes to flucloxacillin DILI, with valine at position 97 being common to both predisposing alleles. Flucloxacillin DILI is rare (incidence about 8.5 per 100000), and over 13,500 people would need to be tested to prevent one case of DILI101.  Therefore prospective testing for *HLA-B\*57:01* prior to flucloxacillin prescription would not be cost-effective. However, typing for *HLA-B\*57:01* may still have diagnostic utility (see below).

**Muscle injury**

Statins are a widely used group of drugs that have been associated with different forms of muscle injury102. In most instances, the muscle injury has been related to a genetic polymorphism in the influx transporter gene *SLCO1B1103*. However, statins can also cause necrotizing autoimmune myopathy, which is relatively rare, and is associated proximal myopathy with creatine kinase levels raised up to 50,000 IU/L102. This form of myopathy can present after years of use of statins, and may persist after stopping the statin, requiring treatment with immunosuppressants. Interestingly, patients with statin-induced necrotizing autoimmune myopathy often have circulating anti-HMG CoA-reductase (HMGCR) antibodies, and this adverse reaction has been associated with *HLA-DRB1\*11:01104*.

**Agranulocytosis**

Agranulocytosis, a reduction in the absolute neutrophil count below 100 neutrophils per microlitre, can be caused by non-immune (usually due to cancer chemotherapy) or immune mechanisms. Antithyroid drugs (propylthiouracil, carbimazole and methimazole) can cause immune-mediated agranulocytosis. The frequency is approximately 0.35%105. Patients are warned to seek medical attention if they experience symptoms that may be indicative of agranulocytosis, which is not ideal (as some patients can become seriously ill and warnings can also lead to patient anxiety.

An early case-control study in Japanese participants106 (24 cases, 68 methimazole-treated controls and 525 healthy controls) showed an association of methimazole-induced agranulocytosis with *HLA DRB1\*08:03* (P=0.007, OR 4.18). A study in a Taiwanese population107 (42 cases and 1,208 Graves' disease controls) confirmed the association with *HLA-DRB1\*08:03* (P=1.83x10-9, OR=6.13). In addition, a significant association was also seen for *HLA-B\*38:02* (P=7.75x10-32, OR= 21.48). For those with both *HLA-B\*38:02* and *HLA-DRB1\*08:03* the odds ratio increased to 48.41. *HLA-B\*38:02* and *HLA-DRB1\*08:03* have been reported as markers for anti-thyroid drug-induced agranulocytosis in these other populations:

* Southern Chinese – 20 cases, 775 controls, *HLA‐B\*38:02:01* was associated with carbimazole/methimazole‐induced agranulocytosis (P=2.5×10‐14, OR = 265.5), but not associated with propylthiouracil108.
* Vietnamese - 21 cases, 81 drug-tolerant controls, *HLA-B\*38:02* was associated with carbimazole/methimazole‐induced agranulocytosis (P=5.2x10-7, OR=28.6)109.
* Han Chinese: 29 cases, 140-drug tolerant controls, associations with *HLA-B\*38:02* (P=2.41×10−4, OR= 7.525), *HLA-DRB1\*08:03* (P=1.57×10−3, OR= 4.316) and *HLA-B\*27:05* (P=1.1x10-4, OR=66.24)110.

Most recently, a study in a Japanese population111 (87 cases and 384 antithyroid drug-treated controls) identified *HLA-B\*39:01:01* (P=1.4×10−3, OR=3.35) as a novel risk-factor for agranulocytosis. This association was replicated in Chinese (P=9.0×10−3), Taiwanese (P=1.1×10−3), and European populations (P=5.2×10−4), with a meta-analysis of pooled results including cases from this and previous studies confirming the importance of this HLA allele (P=1.2×10−9, OR = 3.66). In addition, analysis of the discovery cohort also replicated the association between *HLA-DRB1\*08:03:02* and antithyroid drug-induced agranulocytosis (P=5.2×10−7, OR=2.80).

**Implementing genetic testing into clinical practice.**

***Strength of evidence***: As highlighted in previous sections, there have been many discoveries of genetic factors predisposing to drug hypersensitivity reactions, but implementation into clinical practice has been much slower. Uptake into clinical practice depends on the strength of evidence of the association between a genetic marker and the drug hypersensitivity. In addition, it has become increasingly important to show that introduction of the genetic test will be cost-effective.

The highest level of evidence according to the evidence hierarchy is the randomized controlled trial. A recent systematic review showed that only one randomized controlled trial (RCT) has been undertaken in this area112 - this was the PREDICT-1 trial22 which showed that *HLA-B\*57:01* genotyping was clinically effective in preventing abacavir hypersensitivity reactions. Interestingly, implementation of *HLA-B\*57:01* testing occurred before the completion of the PREDICT-1 trial in some countries such as the UK and Australia, countries that also participated in the study, largely because of the strength of the evidence (from observational studies), demonstration of cost-effectiveness, and a clinical and patient community that was willing to accept innovative change. It is also interesting to note that while testing for *HLA-B\*57:01* was initially reactive (i.e. testing just before prescription of abacavir), this has now become a pre-emptive test, i.e. patients are tested for *HLA-B\*57:01* at the time of HIV diagnosis as part of the initial clinical work-up even if abacavir may not be used as first-line therapy, and the test result kept in the clinical records, for when (and if) abacavir is needed.

Instead of undertaking RCTs, some investigators have undertaken prospective studies where HLA genotyping is undertaken prior to drug prescription, and the culprit drug avoided if the patient is positive for the HLA allele. This requires the use of historical controls, which has its limitations113, including the need to accurately determine the historical incidence of a rare adverse drug reaction. Such prospective studies have focused on carbamazepine (*HLA-B\*15:02* and *HLA-A\*31:01*), allopurinol (*HLA-B\*58:01*) and dapsone (*HLA-B\*13:01*)114 – all have shown that pre-prescription testing for the specific HLA alleles reduced the incidence of hypersensitivity reactions compared with data derived from historical controls.

Most of the other drug hypersensitivity genetic studies which have been reported since 2000 have used a case-control design3. Various genotyping strategies have been used including genome-wide association studies, and some of these have found striking associations, with many of them being replicated in subsequent studies. Such observational studies may not be regarded as providing the strength of evidence needed to implement a genetic test into clinical practice. However, undertaking RCTs in this area is extremely difficult, if not impossible in many cases. This is due to the rarity of the reaction (which would therefore require a large sample size) and difficulty in raising funding because many of the compounds implicated in hypersensitivity reactions are generic drugs. It is our opinion that all types of evidence should be assessed, including observational data, rather than relying on the hierarchy of evidence115, which may have outlived its usefulness. All data should be interpreted in an intelligent fashion to determine whether the evidence is adequate to enable clinical implementation.

***Predictive values:*** Studies of genetic testing often report various diagnostic parameters which indicate the predictive accuracy of the test. A recent systematic review has shown that most of the studies report sensitivity, specificity, positive and negative predictive values, while others also report values for number needed to test to prevent one reaction6. These parameters can vary for the same drug hypersensitivity reaction between different studies. In general, most of the studies have shown that the positive predictive values are low while the negative predictive values and specificity are high but not complete across different ethnicities in particular. This indicates the need to identify other factors (genetic and non-genetic) which increase the risk and therefore the predictive value of genetic testing.

***Cost-effectiveness:*** Determination of cost-effectiveness of a genetic test is an important piece of evidence that may be required by many healthcare systems before the test is taken up into clinical practice, and re-imbursed79. Since different healthcare systems have different models and costing structures, any cost-effectiveness analysis may only be relevant for the country where the data are derived from, and thus the same test may show different levels of cost-effectiveness in different countries. There are many reasons for this including healthcare costs, costs of genetic testing and the population prevalence of the implicated genetic variant79. The latter can lead to policies which lead to recommending genetic testing in one ethnic group but not in another ethnic group within the same country. For example, in Singapore, a policy for genotyping of *HLA-B\*15:02* prior to carbamazepine prescription was introduced for the Chinese and Malay populations based on cost-effectiveness analysis, but not for Indians116. This has the potential to introduce racial inequalities and inequity in access to care.

***Drug labels and guidelines:*** Inclusion of a genetic test in the drug label will aid implementation. However, the information in the drug label can vary from a test that is mandated or recommended (which represents the minority) to a test which is included for information only. In most cases, the latter is ignored, and the evidence required for transitioning from an “information” label to a “recommended” label is not clear. Furthermore, there is lack of harmonization in the wording used in drug labels from different regulatory agencies117, including when it comes to accurately identifying the at-risk populations based on self-reported ethnicity.

In order to aid implementation, several groups have started to develop guidelines, the two most well-known being the CPIC118 and the Dutch Pharmacogenetics Working Group (DPWG)119. This can lead to discordance between the guidance present in the drug label compared to the guideline. For instance, the CPIC guideline suggests that both *HLA-B\*15:02* and *HLA-A\*31:01* should be considered when prescribing carbamazepine36, while the FDA and EMA drug label recommend testing for *HLA-B\*15:02* but include *HLA-A\*31:01* for information only.

***Behaviour change***: Changing the behaviour of healthcare professionals is important in implementing a new test for drug hypersensitivity. This has been highlighted with respect to *HLA-B\*15:02* testing to prevent carbamazepine hypersensitivity: physicians either did not undertake the testing as recommended or avoided the use of carbamazepine and prescribed alternative drugs, which also had a high risk of the hypersensitivity reactions (figure 2)120-122.

Clearly, education and improving the knowledge of healthcare professionals is important in changing behaviour thereby increasing the uptake of pharmacogenetic testing. In the future, as more pharmacogenetic tests become implemented into clinical practice, developing decision support systems will be important to ensure that the relevant populations are tested, and test results are interpreted accurately.

***Novel uses for genetic testing:*** Most genetic tests have been developed to predict susceptibility to an adverse drug reaction. However, it is possible to use genetic tests for other purposes as outlined in our framework for genetic testing123:

* Use in diagnosis: a genetic test which has a 100% negative predictive value could be used to improve the diagnosis of a drug hypersensitivity reaction and differentiate it from a non-drug induced disease. For example, *HLA-B\*57:01* has a 100% negative predictive value in relation to flucloxacillin-induced liver injury. Thus, it could be used to differentiate flucloxacillin-induced liver injury from another cause of abnormal liver function tests, for example gallstones, to ensure that the patient not only receives appropriate treatment, but also appropriate advice on whether to avoid flucloxacillin in the future.
* Stratification of monitoring: Many drug labels recommend blood test monitoring after starting a drug. This is inconvenient, costly and unnecessary for most of the patients. Identification of a susceptible group using a genetic test may allow stratification of monitoring so that the susceptible group is monitored more frequently, while non-susceptible individuals are monitored less frequently. This strategy only works in drugs where a genetic factor has a high negative predictive value.

***Genetic testing technology***: In the past, the lack and cost of genetic testing was often used as an excuse for not undertaking pharmacogenetic testing. However, with the advances in genotyping technologies, and the associated reduction in costs, this is no longer a viable excuse. The COVID-19 pandemic has shown that it is possible to implement genetic testing at scale in the community124. Currently, for most genetic tests, a reactive strategy is used, usually testing for a single locus prior to drug prescription. This requires waiting for the test result prior to prescribing the drug, which itself acts as a barrier to pharmacogenetic testing. We therefore need to move from a reactive to a pre-emptive strategy. This is starting to be implemented in some sentinel sites. For example, Boston Children’s Hospital has been using a four-HLA (*HLA-A\*31:01, HLA-B\*15:02, HLA-B\*57:01*, and *HLA-B\*58:01*) panel-based test for years125. We have developed a globally relevant 23 HLA allele panel which has analytic validity equivalent to that of sequence-based typing, has a turnaround time of approximately 48 hours, has an accompanying decision support system, costs less than single locus testing, and is cost-effective126. The panel can be used when a particular HLA allele test is needed, with the other HLA allele results being stored in the patient’s health record for use later if the patient is prescribed the relevant drugs, thus moving from a reactive to a pre-emptive approach.

**Summary**

There is increasing evidence that genetic factors and primarily HLA class I alleles, are important in predisposing to drug hypersensitivity reactions. Much of the research has focused on discovery, with many associations having been identified since the beginning of this century. This excellent work needs to continue and should be stepped by (a) using newer technologies such as whole human genome sequencing to identify novel genetic factors; (b) increasing international collaboration to increase the breadth and depth of patients and drugs evaluated; and (c) identifying genomic predisposing factors both within and outside the HLA region, including those which interact with HLA alleles to modulate the risk of hypersensitivity. By comparison to discovery, the application of genetic findings into clinical practice has lagged. Further work in this area is essential over the next few years to realize the promise of novel genetic discoveries and make a real impact on patient outcomes.

**Clinical Care Points**

* A patient who develops features of a hypersensitivity reaction should be carefully evaluated for both the clinical manifestations and drug causality. This will help to reach the correct diagnosis, identify the culprit drug, and recruit to studies on drug hypersensitivity.
* Before prescribing a drug, the clinician should be aware of the propensity of that drug to cause hypersensitivity, and whether there are any clinical, genetic and other factors increasing susceptibility to that reaction. Risk mitigation should be undertaken by minimizing clinical risk factors and undertaking any genetic tests, as appropriate.
* Genetic tests may sometimes be helpful in a patient who has developed a hypersensitivity reaction when the etiology is unclear; for example, when the patient has been started on multiple drugs, and it is difficult to identify the culprit, and when there is an alternative co-existing non-drug induced cause of the same clinical manifestations.

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**Boxes**

**Box 1**

**Some caveats about HLA associations with drug hypersensitivity reactions**

* Although strong associations have been identified with many drug hypersensitivity reactions and HLA alleles, the possession of an allele does not mean that the individual will develop the reaction (resulting in a low positive predictive value)6. This is not fully understood (see box 2).
* The same drug and the presence of the same HLA allele can lead to different clinical manifestations in different individuals. For example, *HLA-A\*31:01* has been associated with different phenotypes of carbamazepine hypersensitivity (maculopapular exanthem, DRESS, and drug-induced liver injury)7. The mechanism of this is unclear.
* For reasons which are unclear, the clinical severity of a reaction can vary between different individuals despite being exposed to the same drug, and carrying the same HLA allele.
* Different HLA alleles can predispose to hypersensitivity reactions to the same drug in different ethnic groups, which largely relates to the population frequency of that HLA allele. For example, *HLA-B\*15:02* is associated with carbamazepine-induced Stevens-Johnson Syndrome in South-East Asian populations but not in Northern European populations, where *HLA-A\*31:01* is more important8.
* One HLA allele can be associated with different types of hypersensitivity reactions with many different drugs. For example, *HLA-B\*57:01* is associated with abacavir hypersensitivity syndrome9, carbamazepine associated Stevens-Johnson Syndrome in European ancestry populations7, flucloxacillin-induced liver injury10, and pazopanib-induced liver injury11.

**Box 2**

**Factors which modulate the frequency of occurrence of hypersensitivity reactions**

***Underlying disease factors***

* Patients with HIV have an increased risk of hypersensitivity reactions with certain drugs such as sulfonamides but this can be ameliorated by controlling their disease using combination antiretroviral therapy12.
* Patients with cystic fibrosis are at higher risk of hypersensitivity reactions with antibiotics received multiple times during the course of their illness13.
* Patients with cancer being treated with immune checkpoint inhibitors have a higher risk of hypersensitivity reactions to concomitant drugs despite the fact that they may have been previously tolerant to these drugs14.
* *HLA-B\*58:01* increases the risk of allopurinol-induced serious cutaneous adverse reactions, but this risk increased further in patients with co-existing renal impairment15.

***Other genetic factors***

* Besides the presence of the predisposing HLA allele, other HLA alleles carried by the individual may either co-operate and increase the risk or may protect against the hypersensitivity reaction5.
* Polymorphisms in drug metabolising genes may affect the pharmacokinetics of the drug and its metabolites, and thereby increase the risk of hypersensitivity. The best example of this is predisposition to phenytoin-induced serious cutaneous adverse reaction by the low-activity *CYP2C9* variant, *CYP2C9\*316*.
* Specific T-cell receptor clonotypes may interact with specific HLA alleles and increase the risk of a drug hypersensitivity reaction, as shown for carbamazepine17.
* Genes encoding enzymes involved in peptide processing prior to HLA loading may modulate the risk as shown for nevirapine18 and abacavir19.

**Tables**

**Table 1: Associations of abacavir hypersensitivity with *HLA-B\*57:01* in different ethnic groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **HLA allele** | **Region/Ethnicity** | **Reference** |
| Abacavir | *HLA B\*57:01* | Western Australia (White) | 9 |
| North America (majority White, also Black, American Hispanic and other) | 24 |
| North America (majority White, also Hispanic and other). | 25 |
| Spanish (White) | 26 |
| French (majority White, black). | 27 |
| White (majority), Arabic, Black, American Indian/ Alaskan native, mixed other. | 22 |
| North America (White and Black) | 28 |
| North America (majority White, others including Blacks, aboriginals, Indo-Asians, Hispanics, Metis and Orientals and unknown). | 29 |
| European descent (majority White) | 30 |
| United Kingdom (White) | 31 |
| Switzerland (White, Black and other) | 32 |
| White, African American and other (American-Indian, Asian). | 33 |
| White, African-American, Hispanic | 34 |

**Table 2: Studies reporting the association of different phenotypes of carbamazepine hypersensitivity with HLA alleles**.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **HLA allele** | **\*Hypersensitivity reaction** | **Ethnicity** | **Reference** |
| Carbamazepine | *HLA-B\*15:02* | SJS/ TEN | Han Chinese | 38 |
| SJS/ TEN, HSS, MPE | Han Chinese | 39 |
| SJS/ TEN/ HSS | Han Chinese | 40 |
| SJS | Thai | 41 |
| SJS | Indian | 42 |
| SJS/ TEN | Malay, Chinese, Indian | 43 |
| SJS/ TEN | Han Chinese | 44 |
| SJS/TEN | Southern Han Chinese | 45 |
| SJS/ TEN | Thai | 46 |
| SJS | Malay/ Chinese | 47 |
| SJS/ TEN | Han Chinese | 48 |
| SJS/ TEN | Han Chinese | 49 |
| SJS/ TEN | Indian | 50 |
| SJS/ TEN | Han Chinese | 51 |
| SJS/ TEN | Javanese/ Sudanese | 52 |
| SJS/ TEN and MPE | Thai | 53 |
| SJS/ TEN | Han Chinese | 54 |
| SJS/TEN | Thai | 55 |
| SJS | European, Asian, African, Aboriginal, mixed and unknown | 56 |
| SJS | Han Chinese | 57 |
| SJS/TEN | Han Chinese | 58 |
| SJS/ TEN | Malay, Chinese | 59 |
| SJS/ TEN | Southern Indian | 60 |
| SJS/TEN | Han Chinese | 61 |
| SJS | Han Chinese | 62 |
| SJS/TEN | Han Chinese | 63 |
| SJS/TEN | Malay, Chinese | 64 |
| SJS/TEN | Han Chinese | 65 |
| SJS/TEN | Vietnamese | 66 |
| SJS/TEN | Han Chinese | 67 |
| SJS/TEN | Malay, Chinese, Indian | 68 |
| Carbamazepine | *HLA-A\*31:01* | MPE/ HSS | Han Chinese | 39 |
| MPE, erythroderma, DIHS, and other drug eruptions. | Japanese | 69 |
| HSS, MPE | Northern European | 70 |
| SJS/ TEN/ DIHS | Japanese | 71 |
| HSS | Koreans | 72 |
| SJS/TEN, DIHS, EEM, MPE | Japanese | 73 |
| HSS, MPE | European, Asian, African, Aboriginal, mixed and unknown | 56 |
| DRESS | Europeans, Chinese | 51 |
| DRESS/ MPE | Han Chinese | 63 |
| DRESS | Tunisian | 74 |
| SCAR | European | 7 |
| MPE | North Indian | 75 |
| DRESS | European | 76 |

\*Phenotype described as per the original study. SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis, DRESS: drug reaction with eosinophilia and systemic symptoms; HSS: hypersensitivity syndrome; DIHS: drug-induced hypersensitivity syndrome: SCAR: serious cutaneous adverse reaction; MPE maculopapular exanthem; EEM, Erythema exudativum multiforme.

**Table 3. Associations between allopurinol induced cutaneous reactions and *HLA-B\*58:01***

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | HLA allele | \*Hypersensitivity reaction | Ethnicity/region | Reference |
| Allopurinol | *HLA B\*58: 01* | HSS, SJS, TEN. | Han Chinese | 77 |
| SJS/ TEN | Japanese | 80 |
| DRESS/ SJS/ TEN | Han Chinese | 81 |
| MPE/ DRESS/ SJS/ TEN | Han Chinese | 82 |
| SJS/ TEN | Koreans | 83 |
| DRESS/ SJS/ TEN | Portuguese | 84 |
| MPE/ DRESS/ SJS/ TEN | Han Chinese | 85 |
| EEM/ SJS | Japanese | 73 |
| EEM/ DRESS/ SJS/ TEN | Han Chinese | 86 |
| MPE/ DRESS/ SJS/ TEN | Han Chinese | 87 |
| HSS/ SJS/ TEN | Koreans | 88 |
| HSS/ SJS | Koreans | 89 |
| SJS/ TEN | Italian (Caucasian) | 90 |
| SJS/ TEN | Thai | 91 |
| SJS/ TEN | Japanese | 92 |
| SJS/ TEN | European (majority), African, Asian, South American. | 93 |
| MPE/ DRESS/ SJS/ TEN | Thai | 94 |
| DRESS/ SJS/ TEN | Thai | 95 |

\*Phenotype described as per the original study. SJS: Stevens-Johnson Syndrome; TEN: toxic epidermal necrolysis, DRESS: drug reaction with eosinophilia and systemic symptoms; HSS: hypersensitivity syndrome.

**Figure legends**

***Figure 1***

Some of the many different organ systems which can be affected in hypersensitivity, either in isolation or in combination.

***Figure 2***

Three studies120-122 from SE Asia which have highlighted some of the difficulties in implementing genetic testing for *HLA-B\*15:02* in prevent carbamazepine-induced Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) at a country level.