**PRECISION MEDICINE IN DRUG SAFETY**

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**ABSTRACT (100-120 Words)**

Over the past two decades, our understanding of genetic heritability has been derived from candidate gene and genome-wide studies looking at common allelic variant associations. As our access to advanced genomics technologies increases, so too does the availability of pharmacogenomic data for predicting the risk of ADRs. We now have the ability to look at the contribution of rare and even personal genomic variants on ADR risk. However, the increase in data will be accompanied by challenges in interpretation and implementation. This review looks at the current position of drug safety pharmacogenomics and discusses the challenges, as well as some possible future directions.

**INTRODUCTION**

Over the past 20 years, the field of pharmacogenomics has identified a significant number of genetic associations with adverse drugs reaction across a wide range of clinical disciplines. In a number of cases, these associations have been shown to have demonstrable clinical utility, and some have been categorised as mandatory prior to drug administration in order to avoid severe ADRs. However, a there a significant number of associations, whilst compelling, do not currently have the threshold of evidence to justify translation into clinical practice. This review will highlight recent advances in this area focusing on genetic variants which have made it into mainstream healthcare provision for the prevention of ADRs and others whose use is still contentious. In addition, future considerations for discovery and implementation of genomics for prediction of ADRs (Figure 1) will be discussed.

**Pharmacogenomics of ADVERSE DRUG REACTIONS.**

Around the turn of the millennium, our understanding of genetic variation and risk of adverse drug reactions gathered pace. Candidate gene studies (based on *a priori* knowledge of a drug’s pharmacokinetics and pharmacodynamics) advanced our understanding of interindividual variation in drug PK and type A (augmented) ADRs beyond the use of probe-drug assays. However, this gave us little information of the genetic risk factors for idiosyncratic (Type B) reactions. Although there had been studies on the role of the major histocompatibility complex on the short arm of chromosome 6 in predisposing to type B reactions prior to 2000, it was not until this century that more precise molecular characterisation in this region has led to the identification of a substantial number of HLA alleles associated with a range of immune-mediated ADRs. This was seen initially with carbamazepine [1,2] and abacavir [3] through candidate gene approaches but the emergence of genome wide associations study led to identification of many others including novel HLA allele associations for carbamazepine [4,5]. In the last 3 years alone, there have been 28 genome wide association or exome sequencing studies seeking to identify novel genetic risk loci for ADRs (Table 1).

The completion of the human HapMap project [6] facilitated the development of genome-wide association studies and these have proved crucial as an unbiased approach to identifying genetic loci associated with ADRs. Perhaps, one of the best examples of this is the identification of an association between variation in the *SLCO1B1* gene and risk of simvastatin-induced myopathy [7]. This revealed a previously unknown mechanism by which dysfunctional hepatic uptake of statins by organic anion transporter protein 1B1 (OATP1B1) results in increased systemic exposure and risk of myopathy [8].

A combination of candidate gene and genome-wide association and HLA-allelotyping studies have produced the body evidence we have today relating to genetic risk factors for both type A and type B ADRs. Furthermore, some of these gene-drug interactions have clear guidance on their use as pre-emptive clinical tests for prevention of ADRs and some (for example for abacavir hypersensitivity) are even mandated in healthcare settings prior to administration of the drug.

The clinical utility of *TPMT* genotyping for prediction of thiopurine-induced myelosuppression and dose reduction has long been established [9], particularly in Caucasian populations. In recent years, *NUDT15* genetic variability has emerged which is clinically utilised for the same purpose but until recently was thought to be applicable primarily in Asian populations [9]. TPMT functional variants are observed in only 25% of Europeans with thiopurine-induced myelosuppression [10,11] suggesting that other genetic risk factors may exist. However, recent studies have shown that carriage of NUDT15 variants in Europeans also confers an increased risk of myelosuppression in inflammatory bowel disease patients receiving azathioprine which is independent of TPMT genotype and dose [12]. Further validation of these findings is required but NUDT15 variation may explain a significant amount of the missing hereditary in Europeans experiencing thiopurine-induced myelosuppression. Furthermore, a recent massively parallel sequencing study of 2,398 IBD or ALL patients [13] identified 1,152 deleterious variants which greatly improved prediction of thiopurine toxicity and accuracy of pharmacogenetic-guided dosing individualisation. This highlights how, even a pharmacogenetic test which has long been clinically implemented, such as TPMT/NUDT15 and thiopurines, could be significantly improved by the application of advanced genomic technologies and truly individualised by incorporating rare and personal variant data into clinical decision support algorithms.

Rare Variants

Our understanding of the genetic predisposition to ADRs has to date been largely derived from associations with common variants (with a minor allele frequency (MAF) >1%). As our understanding of human genetic variation has advanced, aligned with ever cheaper and more accessible genomic technologies, the role of rare (defined as MAF<1% [14]) or unique variants has started to emerge. It has been estimated that each of us has between 40K and 200K variants which have a population MAF<0.5% [15] and so it is not inconceivable that some of these may make us uniquely genetically predisposed to both type A and type B ADRs.

For type A ADRs, it’s reasonable to suggest that, with a few notable exceptions, research identifying PK-related drug-gene interactions for common allelic variants has had limited impact in terms of clinical utility. Studies now are looking to determine the significant missing heritability for ADR risk which could be explained by rare or even private variants. A recent analysis showed that 93% of all single nucleotide variants (SNVs) in 146 pharmacogenes influencing drug disposition were rare [16] and within these 146 pharmacogenes, an individual of European or African ethnicity carries an average of 101 and 121 SNVs, respectively. It is thought that rare variants may contribute 30-40% of genetically-derived inter-individual variability in the function of a gene [16,17].

Studies of rare variants in genes for which *a priori* knowledge of impact on drug disposition exists are already enhancing our understanding of missing ADR risk heritability. CYP3A4 variation and taxane-induced peripheral neuropathy was an early example of this. Next-generation sequencing has identified deleterious rare variants in *CYP3A4,* the key hepatic enzyme in taxane metabolism which are associated with an increased frequency and severity of paclitaxel-induced peripheral neuropathy (PN) [18]. Previous studies of common *CYP3A4/5* variants and taxane PN had yielded inconsistent findings and failed to explain a significant proportion of genetic heritability [19-22].

Muscle toxicity or myopathy is often associated with statin administration. There are many different definitions of statin myopathy, one of which is based on a rise in serum creatine kinase (CK) of >4x the upper limit of normal (ULN) [23]. The incidence is estimated to be 5/100,000 patient years [24] with the more severe rhabdomyolysis phenotype (CK>10xULN and renal impairment) estimated to have an incidence of 0.3-8.4/100,000 patient years [25]. It is now accepted that there is an association between simvastatin-induced myopathy and a non-synonymous SNP (p.V174A) in Solute Carrier Organic Anion Transporter Family Member 1B1 (*SLCO1B1*), a gene encoding the hepatic drug uptake transporter organic anion transporter protein 1B1 (OATP1B1) [26]. The underlying biological basis of this association is that carriage of p.V174A increases systemic exposure to simvastatin [8] which in turn increases the risk of myopathy. Guidelines from the Clinical Pharmacogenetics Implementation consortium (CPIC) recommend that for individuals who carry 1 or more copies of the low function *SLCO1B1* alleles, a lower dose of simvastatin or an alternative statin (pravastatin/ rosuvastatin) should be prescribed and CK monitoring considered [27].

*SLCO1B1* variants are also associated with methotrexate clearance, particularly in paediatric acute lymphoblastic leukaemia where 10.7% of the variability can be explained by *SLCO1B1* variation, of which ~20% was attributed to rare variants [28]. It is therefore conceivable that, for simvastatin-induced myopathy, rare *SLCO1B1* variants might also contribute to risk. However, a recent exome sequencing study of 2 independent cohorts failed to identify any rare variants in *SLCO1B1* that were associated with either generalised (CK>4xULN) or severe myopathy (CK>10xULN/ rhabdomyolysis) [29]. Indeed, a recent GWAS [30] and the exome sequencing study [29] also failed to identify other novel genetic loci beyond *SLCO1B1* that predispose to statin myopathy. Recent functional work has focused on the role of statins on mitochondrial function in the pathogenesis of myopathy [31]. It is therefore possible that predisposition to statin-induced myopathy may also be due to mitochondrial mutations, but this needs further investigation.

*Immune-mediated ADRs*

The association between HLA-B\*57:01 and abacavir hypersensitivity, first reported in 2002 [3], has been held up as an exemplar for the translation of pharmacogenetics into clinical practice. Mandatory pre-emptive HLA-B\*57:01 allelotyping was rapidly adopted into healthcare around the world based on compelling evidence demonstrating i) a profound effect on reducing the incidence of hypersensitivity from ~5% to <1% [32] and ii) clear cost-effectiveness in healthcare settings [33]. However, it is important to note that possession of the HLA-B\*57:01 allele is neither sufficient nor necessary to lead to abacavir hypersensitivity. Two recent studies have shed further light on this. First, in an evaluation of 85 out of 1769 HLA-B\*57:01 negative individuals, re-challenge of 8 patients resulted in 7 experiencing a further reaction [34]. Thus, in these individuals, genetic factors other than those mediated by HLA-B\*57:01 may be important. Second, and conversely, not all patients who carry the HLA-B\*57:01 allele develop abacavir hypersensitivity. A recent analysis has shown that abacavir hypersensitive patients who were HLA-B\*57:01 positive were less likely than tolerant individuals to carry a genetic variant within the endoplasmic reticulum aminopeptidase 1 (ERAP1) gene [35]. ERAPs are a group of proteins which are involved in antigenic peptide trimming prior to loading into HLA- class I molecules and potentially alter the expression of HLA class I risk alleles. Interactions between ERAP and HLA class I mediated auto-immune conditions, specifically ankylosing spondylitis, have previously been reported [36]. These data indicate that more efficient peptide trimming in combination with HLA-B\*57:01 is required to trigger a hypersensitivity reaction to abacavir [35], and is also consistent with a similar finding for nevirapine-induce SJS/TEN in sub-Saharan African populations [37].

There is a strong association between HLA-B\*15:02 and the occurrence of carbamazepine-induced Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) in South East Asian populations [2,38]. However, not all patients who carry the risk allele develop SJS/TEN with carbamazepine. A recent study in such patients identified preferential public T-cell receptor usage [39], with the α and β clonotypes being expressed by cytotoxic T lymphocytes that are known to be important in the pathogenesis of SJS/TEN. This finding highlights the importance of the immunological synapse that is formed at the initiation of an immune reaction between the HLA allele, T cell receptor and drug-derived antigen.

Prospective studies to demonstrate that pre-prescription genotyping of HLA alleles to prevent serious immune-mediated ADRs have now been completed with abacavir (HLA-B\*57:01) [40], carbamazepine (HLA-B\*15:02 [41] and HLA-A\*31:01 [42]), allopurinol (HLA-B\*58:01) [43,44], and most recently with dapsone (HLA-B\*13:01) [45]. Health economic analysis has also shown that genotyping for certain HLA alleles, such as HLA-A\*31:01 prior to carbamazepine use [46], and HLA-B\*58:01 prior to allopurinol use [44] may be cost-effective, but only in certain populations where the risk allele has a high population prevalence. Panel tests which genotype for multiple HLA alleles have also been shown to be cost-effective [47]. Increasing use of whole genome sequencing in the clinic will also provide data on the HLA profile of individual patients in the future, but the key factor will be to ensure that clinical decision support systems are developed which can provide interruptive alerts in patients with risk alleles at the point of prescribing.

Genetic studies in the last 3 years have identified a significant number of new HLA allele-drug associations (Table 2). Many of these are entirely new gene-drug interactions, but some such as the association between HLA-B\*57:01 and carbamazepine-induced SJS/TEN in Caucasians [48,49] highlight the complexity of gene-phenotype-ethnicity interactions with the same drug providing insights into the pathogenesis. This is also exemplified by the recent finding of an association between Protein tyrosine phosphatase non-receptor type 22 (*PTPN22*) and liver injury in a multi-ethnic cohort caused by a number of drugs [50]. *PTPN22* is a well-established risk locus for a number of autoimmune conditions including rheumatoid arthritis [51], systemic lupus erythematosus [52] and autoimmune thyroid disease [53]. The missense variant in *PTPN22* increased the risk of liver injury, independent of the HLA predisposition, by approximately 40% suggesting that immune dysregulation is also needed on top of the HLA association to lead to tissue injury.

**Pre-emptive Testing**

It has been estimated that 99% of the population have at least 1 actionable pharmacogenomic variant within 13 key pharmacogenes [54]. Based on this, and other comparable observations, a number of initiatives have utilised panel-based pharmacogene testing and assessed implementation into healthcare settings. These include PREPARE [55], ACCOuNT [56] , eMERGE [57] , IGNITE [58] and PG4KDS [59]. Each of these studies is limited to a small number of well-validated pharmacogenes associated with patient variability to drug response with the aim of demonstrating clinical utility and benefit across a range of clinical disciplines. Moving forward, there is a world-wide interest in determining how whole-genome sequencing can be utilised in clinical practice. For instance, there are at least 14 nations with government funded genomic medicine programmes [60]. This will increase the number of individuals having their genome sequenced and enhance the amount of pharmacogenomic data available to the prescribing physician. However, with this vast amount of genomic data available to healthcare professional for each patient, comes a critical need to provide adequate clinical decision support systems [61]. Despite the clear obstacles, access to such data, aligned with clarity of interpretation to aid implementation will enhance our ability to predict and prevent ADRs. For instance, for some gene-drug interactions, genotyping at the time of patient consultation would be deemed to be impractical for most patients because of the sheer number of patients being prescribed the drug. However, this would become practical if the genetic information were already available. An example of this is *CYP2D6* and codeine. Codeine is metabolised to pharmacologically active morphine by hepatic cytochrome P450 2D6 (CYP2D6). Individuals who are CYP2D6 poor metabolisers (5-10%) will not be able to form the active morphine metabolite and will therefore have little or no pain relief. By contrast, ultra-rapid metabolisers (URM; 1-30% depending on ethnicity) will form excessive amounts of morphine, which may lead to respiratory depression [62], as has been reported in a breast-fed neonate where the mother was a CYP2D6 URMs [63].

**Polygenic risk scores**

Many of the well validated genetic risk factors for ADRs demonstrate heritability with a large effect size, often determined from very small patient cohorts. HLA-B\*15:02 carriage and risk carbamazepine-induced severe cutaneous reactions, for example, has an estimated odds ratio of 27.33 (95%CI 9.93-51.17) [64]. For many other ADRs, the effect size is likely to be much smaller and dependent on a number of low penetrant genes, similar to that seen for complex diseases such as diabetes and coronary artery disease. This has seen the emergence of polygenic risk scores utilising a large number of variants of differing penetrance (and therefore weighted accordingly) to determine an individuals’ disease risk. Potentially, such methodology be applied to pharmacogenomics to identify polygenic prediction to drug response phenotypes.

It should be noted that for complex diseases, the cohort sizes utilised to identify low effect variants and develop PRSs are often in the tens or hundreds of thousands. For rare ADRs, cohorts of this size would be extremely challenging to achieve. However, examples of the utilisation of PRSs for the prediction of drug-induced adverse events are emerging, such the report of a PRS derived from 61 common variants which was predictive of drug-induced torsade de pointes [65]. The potential for utilising PRSs to predict ADRs is promising and therefore merits further investigation, but will require new, collaborative recruitment strategies to attain sufficient case numbers.

**BEYOND HUMAN PHARMACOGENOMICS**

Predisposition to ADRs is due to a combination of clinical and genetic risk factors, but the accuracy of prediction varies with the drug and the patient. An area which needs further investigation is the role of the microbiome in drug safety. One key example of this is the colorectal cancer drug irinotecan. The gut microbiome has been implicated in delayed-type diarrhoea attributable to irinotecan. The active (and toxic) metabolite of Irinotecan (SN-38) is glucuronidated by UGT1A1 to SN-38G to facilitate excretion in the faeces. It has been shown that SN-38-G can be de-glucuronidated back to active SN-38 by bacterial β-glucuronidases in the gut lumen, and this may be responsible for delayed irinotecan diarrhoea [66]. Studies of healthy stool samples have also identified low and high ex vivo faecal metaboliser phenotypes for irinotecan de-glucuronidation [67].

There is increasing evidence of the role of the microbiome in drug disposition. A recent study identified 30 microbiome-encoded enzymes that collectively converted 20 orally administered drugs to 59 metabolites [68]. Furthermore, the metabolome-derived from the gut microbiome has also been shown to have a significant impact on an individual’s drug metabolism [69]. Future studies should therefore also consider pharmacomicrobiomic and pharmacometabolomic variability, in addition to inherited variability in our genomes.

**THE Future**

Though a significant number of HLA-allele associations with immune mediated ADRs have been identified (table 2), there are many questions which remain unanswered. For example, despite possessing the same genetic risk factor, we do not fully understand what predisposes some individuals to present with more severe phenotypes (e.g. SJS/TEN) rather than milder rash phenotypes. Are some individuals predisposed to SJS/TEN *per se*? Genome-wide associations studies have sought to identify generalised SJS/TEN risk factors but have largely been inconclusive [70,71]. Furthermore, the same drug (the HIV drug nevirapine, for example) can lead to different ADR phenotypes in different tissues (skin and liver) with different genetic risk factors for each (HLA-C\*04:01 in skin [72,73] and HLA-DRB1\*01:01 [74]). It is possible that this variability is due to tissue-specific differential regulation of class I and class II HLA proteins and/or tissue-specific drug metabolism. Thus, further research is needed to understand factors predisposing individuals to sub-phenotypes of ADRs [75]. The challenge will be to identify and recruit adequate numbers of patients with different ADR phenotypes associated with the same drug, which will require co-ordinated global efforts.

Although many drug-HLA gene associations have already been identified, there are many drugs where no genetic predisposing factors have yet been identified. For instance, a 2015 study which text-mined the FDA drug label database identified 259 small molecules or biologics which had SJS/TEN noted as a potential ADR [76]. For many therapeutics, these reactions are rare (1 case per million new users in the case of ibuprofen[75]) but, given the sheer number of people taking some of these drugs, numbers worldwide are likely to be significant. Novel approaches to identify patients with these serious ADRs is going to be required, and this should include not only international collaborations, as already mentioned, but also use of AI techniques such as natural language processing to identify cases through electronic healthcare records, use of alternative sources of patient materials such as DNA from histopathology archives (with adequate clinical phenotype data), and working with disease-specific patient groups to identify patients via social media.

Our understanding of immune-mediated ADRs is built on the assumption that the drug is acting in some way as the antigen, via one of three possible mechanisms: hapten/pro-hapten; pharmacological interaction (p-i) or altered peptide repertoire mechanisms. However, we now need to consider alternative mechanisms with the advent of immunotherapies which are increasingly being used in cancer and in diseases such as multiple sclerosis. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies targeting 3 distinct proteins, which have a key role in regulating the immune system: PD-1 (e.g. pembrolizumab), PD-L1 (e.g. atezolizumab) and CTLA-4 (ipilimumab). Although these novel therapies have been transformational for some patients and for some types of malignancy, their use is also associated with a significant incidence of immune-mediated ADRs. These can affect many organ systems with the most frequently observed manifestations for the PD-1 inhibitor pembrolizumab affecting endocrine (15%), skin (9%), gastrointestinal (diarrhoea (7%)/ colitis 1%)), and pulmonary (5%) [77] systems. For the CTLA4 inhibitor ipilimumab, the ADR incidence appears higher and phenotype profile subtly different [78]., and the situation is being further complicated by the use of these drugs in combination, not only with each other, but also with conventional cytotoxic agents, which will change both the profile and frequency of adverse events. The mechanisms underlying these reactions are not fully understood, and further work would help to improve the benefit-harm ratio of these novel medicines in to order to increase their use and to stop early discontinuation in those patients showing benefit but with intolerable adverse effects.

In conclusion, there has been significant progress over the last few years in identifying genetic factors predisposing to serious adverse reactions, which has also contributed to a better understanding of mechanisms. However, much more remains to be done. It is likely that what has been uncovered so far is the “low-hanging fruit”, and to identify the “fruit higher up the tree”, more novel methodologies for both patient identification and mechanistic understanding will be needed to reduce the burden of ADRs.

**FIGURE LEGENDS**

Figure 1. Pharmacogenomics of ADRs- the putative pathway from discovery to implementation.

**Table 1.** Recently identified Genetic associations with ADRs from Genome-Wide Association and Whole Exome Sequencing (WES) Studies (last 3 years).

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Drug** | **Indication** | **ADR** | **Significant Associated Loci/Alleles** | **GWAS** | **WES** | **Ref** |
| ACE inhibitors | Hypertension | Cough | Multiple | Y |  | [79] |
| ACE Inhibitor/ ARBs | Hypertension | Angioedema | *F5* |  | Y | [80] |
| ALL Induction therapy (including asparaginase) | Acute Lymphocytic Leukaemia | Hepatotoxicity | *PNPLA3* rs738409 | Y |  | [81] |
| Asparaginase | Acute Lymphoblastic Leukaemia | Hypersensitivity | *CNOT3* | Y |  | [82] |
| Carbimazole/methimazole | Hyperthyroidism | Cutaneous reactions and/or hepatoxicity | *RGS9,MMP20* | Y |  | [83] |
| Carbamazepine | Epilepsy | SJS/TEN | *HLA-B\*57:01* | Y |  | [48] |
| Clopidogrel | Anti-platelet | Major Adverse Cardiac Events | N6AMT1  | Y |  | [84] |
| “Cold medicine” | Cold | SJS/TEN | Between *ZNF423* and *CNEP1R1,* REC114, NPTN  | Y |  | [85] |
| Corticosteroids (Inhaled) | Asthma, COPD | Adrenal Suppression | *PDGFD* | Y |  | [86] |
| Dexamethasone | ALL | Osteonecrosis, Thrombosis | *F2RL1* | Y |  | [87] |
| Flucloxacillin | Bacterial Infection | Hepatotoxicity | *HLA-B\*57:01+B\*57:03* | Y |  | [88] |
| Heparin | Anticoagulant | Thrombocytopenia | rs1433265 (chr5) | Y |  | [89] |
| Interferon-β | Multiple Sclerosis | Hepatotoxicity | *IRF6* | Y |  | [90] |
| Isoniazid,rifampicin, pyrazinamide;  | Tuberculosis | Hepatotoxicity | *NAT2, PSD3* | Y |  | [91] |
| Minocycline | Bacterial Infection | Hepatotoxicity | *HLA-B\*35:02* | Y |  | [92] |
| Multiple | - | Hepatotoxicity | *PTPN22* | Y |  | [50] |
| Nevirapine | HIV | SJS/TEN | *HLA-C\*04:01* | Y |  | [72] |
| Pandemrix | Influenza (H1N1) | Narcolepsy | GDNF-AS1 | Y |  | [93] |
| Phenytoin | Carbamazepine | Maculopaplar Exanthema | *CFHR4, CFH* | Y |  | [94] |
| Polyethylene glycol (PEG) | Multiple | Immunogenicity | *IGH* | Y |  | [95] |
| Statin | Hypercholesterolemia | Myopathy | *SLCO1B1* | Y |  | [30] |
| Sulfonylureas | Type II Diabetes | Cardiac QT, JT, and QRS intervals | Multiple | Y |  | [96] |
| TerbinafineSertraline | Fungal InfectionDepression | Hepatotoxicity | *HLA-A\*33:01* | Y |  | [97] |
| Trastuzumab | Breast Cancer | Cardiotoxicity | Multiple | Y |  | [98] |
| Trastuzumab | Breast Cancer | Cardiotoxicity | *EYS* |  | Y | [99] |

**Table 2.** Recently published reports of novel HLA allele-Drug Associations for Immune-Mediated Adverse Drug Reactions

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Drug** | **Indication** | **ADR** | **Associated Allele** | Ref |
| Acetaminophen  | Analgesic/ Anti-pyretic | SJS/TEN | *HLA-B\*13:01/ HLA-C\*14:03* | [100] |
| Carbamazepine | Epilepsy | SJS/TEN | *HLA-B\*57:01* | [48] |
| “Cold Medicine” | Cold | SJS/TEN | *HLA-A\*26:02/ HLA-B\*44:03* | [101] |
| Clozapine | Schizophrenia | Myocarditis | *HLA-C\*07:01* | [102] |
| Co-trimoxazole | Bacterial Infection | SJS/TEN | *HLA-B\*15:02/ HLA-C\*08:01 (Thai)* | [103] |
| Ipilimumab | Melanoma/ Renal Cancer | Hepatotoxicity | *HLA-B\*39:01* | [104] |
| Methimazole | Hyperthyroidism | Hepatotoxicity | *HLA-C\*03:02 (Han Chinese)* | [105] |
| Minocycline | Bacterial Infection | Hepatotoxicity | *HLA-B\*35:02* | [92] |
| Phenytoin | Epilepsy | DRESS | *HLA-B\*56:02 (Aboriginal Australian)* | [106] |
| Raltegravir | HIV | DRESS | *HLA-B\*53:01* | [107] |
| Terbinafine | Anti-Fungal | Hepatotoxicity | *HLA-A\*33:01* | [108] |
| Trimethoprim-sulfamethoxazole | Bacterial Infection | Hepatotoxicity | *HLA-B\*14:01 (European)**HLA-B\*35:01 (African)* | [109] |
| Vancomycin | Bacterial Infection | DRESS | *HLA-A\*32:01* | [110] |

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