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Title:
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Date:
2019-06-01

Citation:
Mullan, K. A., Anderson, A., Illing, P. T., Kwan, P., Purcell, A. W. & Mifsud, N. A. (2019). HLA-associated antiepileptic drug-induced cutaneous adverse reactions. Hla, 93 (6), pp.417-435. https://doi.org/10.1111/tan.13530.

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HLA associated antiepileptic drug-induced cutaneous adverse reactions

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Short title: HLA and antiepileptic drug-induced cADRs

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tan.13530

Conflict of Interest

The authors confirm that there are no conflicts of interest.

Abstract

Adverse drug reactions (ADRs) are a common cause of hospital admissions (up to 19%), with the majority of cases due to off-target predictable drug effects (type A reactions). However, idiosyncratic drug-induced immune activated (type B) reactions contribute to a range of hypersensitivity reactions, with T-cell mediated type IV hypersensitivity reactions mainly manifesting as cutaneous ADRs (cADRs). Aromatic antiepileptic drugs (AEDs), used in the treatment of epilepsy as well as bipolar disorder or neuropathic pain, have been implicated as culprit drugs in a spectrum of pathologies ranging from mild maculopapular exanthema (MPE) to severe and life-threatening conditions including drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These AED-induced cADRs are unpredictable based on pharmacological and clinical factors alone, thereby prompting investigations into genomic contributors mediating risk of pathology. The most strongly associated risk genes identified are from the human leukocyte antigen (HLA) class I alleles, which play a critical role in adaptive immunity by flagging either infected or aberrant cells for recognition by surveying T cells. In the setting of drug hypersensitivity, the immunogenicity of HLA molecules and their peptide cargo can be modulated by interactions with small drug molecules that drive inappropriate T cell responses. This review discusses the current understanding of HLA class I molecules in modifying risk of AED-induced cADRs.

Key words: adverse drug reaction; carbamazepine; genomics; lamotrigine; human leukocyte antigen; oxcarbazepine; phenytoin; transcriptomics

Introduction

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality, responsible for >770,000 injuries or deaths per year in the USA[1], and 5.7-18.8% of hospital admissions in Australia[2]. A recent Australian study showed a rising incidence of ADRs over time and a prolongation of hospitalisation time[3]. To mitigate these growing healthcare costs there is an urgent need for effective prevention of ADRs and better management of patients receiving these culprit drugs. One of the most common types of ADR is the cutaneous ADRs (cADRs), which typically occur in the first 2-3 months of drug use. These range from mild skin rash such as maculopapular exanthema (MPE) that manifests as red macular or papular skin eruptions, to the more severe reactions that have multi-organ/multi-system involvement including hypersensitivity syndrome (HSS) or drug reaction with eosinophilia and systemic symptoms (DRESS), and bullous skin diseases Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)[4]. Both SJS and TEN are characterised by rapidly developing blistering exanthema of macules and target-like lesions accompanied by, to different extents, cutaneous and mucosal detachment. Up to 30% of individuals die from TEN and 5% from SJS, where death is mostly due to sepsis and respiratory distress[5]. Survivors have long-term disabilities including vision loss and scarring. Immediate drug cessation is generally recommended when cADRs develop and, in the cases of SJS/TEN and HSS/DRESS, hospitalisation for intensive treatment[6].

One of the leading classes of medications resulting in cADRs are the aromatic antiepileptic drugs (AEDs), four of which are commonly prescribed; carbamazepine, oxcarbazepine, lamotrigine and phenytoin[7] (Figure 1). Carbamazepine and lamotrigine are

first-line treatments for epilepsy, one of the most common neurological disorders (affecting 3-4% of the population)[8]. Apart from seizure prevention, phenytoin is a standard acute therapy for status epilepticus, a medical emergency characterised by continuous seizure activity[8]. Carbamazepine is also widely used to treat neuropathic pain, and both carbamazepine and lamotrigine are used in the management of bipolar affective disorder. Unfortunately, up to 1 in 10 new patients prescribed these medications will go on to develop MPE[9], whilst the incidences of both DRESS and SJS/TEN have been estimated at 1 in 1,000 to 1 in 10,000[10, 11], with an alarming incidence of 1 in 400 for SJS/TEN in at risk populations (*i.e.* Han Chinese descent)[12].

There have been many investigations of genomic contributions that modulate risk for development of these hypersensitivity reactions. The focus of this review is to highlight the known human leukocyte antigen (HLA) associations modulating risk in AED-induced T cell-mediated cADRs, and discuss the need to contextualise genomic risk factors across broader biological systems to aid our understanding of the mechanisms driving immunopathology.

T cell-mediated delayed hypersensitivity reactions

In general, ADRs are categorised as either type A or type B reactions. Type A reactions account for ~80% of reported cases and are innately linked with drug pharmacology (*e.g.* increased bleeding following treatment with the anti-coagulant warfarin or onset of hypotension from beta-blocker toxicity[13]). Type B reactions are idiosyncratic, immune-mediated and can lead to severe cutaneous pathology[14]. The type B reactions can be further segregated into different hypersensitivities based on their immunopathology, including either

B cell-mediated type I-III hypersensitivity reactions or T cell-mediated delayed type IV hypersensitivity reactions[15], with the latter being the focus of this review.

The delayed type IV hypersensitivity reactions extend across a broad spectrum of pathologies that can be assigned into four sub-classifications. Hypersensitivity reactions of type IVa involve monocyte activation and typically manifest as eczema or contact dermatitis, type IVb encompass eosinophilia with multi-organ involvement (*i.e.* HSS/DRESS), type IVc comprise of $CD4^+$ or $CD8^+$ T cell mediated cytotoxicity resulting in tissue necrolysis (*i.e.* SJS/TEN) and type IVd pathology is caused by infiltration and activation of neutrophils that manifest as acute generalised exanthematous pustulosis (AGEP)[15]. Currently, the milder MPE reaction can be classified into both type IVb and IVc hypersensitivity reactions depending on the composition of immune cells involved[15].

Pharmacogenomic identification of genetic risk factors in AED-induced cADRs

Over the past few decades investigations into the genomic contributors of AED-induced cADRs have revealed significant associations with genes encoding the HLA molecules, cytochrome P450 enzyme (CYP; major metabolic enzyme contributing to detoxification of drugs/toxins)[16, 17] and complement factor H (CFH; an integral part of the complement pathway in innate immunity)[18, 19]. Although, alleles of the *CYP* and *CFH* genes have been associated with modulating the risk of AED-induced cADRs, they will not be discussed further in this review.

The HLA molecules encoded within the human major histocompatibility complex (MHC) play an integral part in the adaptive immune system. The main function of HLA

molecules is to display foreign antigenic peptides on the cell surface for recognition by T cells, resulting in an appropriate immune response to clear either infected (*e.g.* viruses) or aberrant (*e.g.* cancer forming) cells[20]. The *HLA* genes, located on chromosome 6, are segregated into different classes (I, II or III) based on structure and function. Both classical class I (*i.e. HLA-A, -B* and *-C*) and class II (*i.e. HLA-DR, -DQ* and *-DP*) genes display a high degree of allelic polymorphism. This polymorphism is thought to result from population migration patterns as well as being driven by the necessity to respond to an enormous diversity of pathogens[21]. Here, we discuss the significant risk associations of HLA class I alleles with AED-induced cADRs, focussing on *HLA-B*15:02*, *HLA-A*31:01* and *HLA-A*24:02* (Table 1), which are differentially expressed across global populations (Table 2).

AED-induced SJS/TEN and HLA-B*15:02

In 2004, the first report demonstrating a strong association between *HLA-B*15:02* in the Han Chinese population and carbamazepine-induced SJS/TEN (odds ratio; OR 2,504) was published. This seminal study showed that the *HLA-B*15:02* allele was present in 100% of SJS/TEN cases, but in only 3% of carbamazepine-tolerant controls and 8.6% of drug naïve controls, equating to 97% specificity and 100% sensitivity[22] (Table 1). Over the past decade, numerous studies have corroborated this association not only in Han Chinese populations[23-33], but also in Thai[34-36], Indian[37-39], Vietnamese[40], Malaysian[41], Spanish Romani[42], Javanese/Sudanese[43], and other[44, 45] populations (Table 1). Conversely, investigations of *HLA-B*15:02*-restricted carbamazepine-induced SJS/TEN in European and Japanese studies[46, 47] failed to find a significant association (Table 1)[29,

46], which is not surprising given the relatively low frequency of this HLA allele in these populations (Table 2). In addition, a carbamazepine structural derivative, oxcarbazepine, also exhibited a similar *HLA-B*15:02* risk association with SJS/TEN in Han Chinese[48], Taiwanese of Han Chinese descent[49] and Thai[49] populations (Figure 1, Table 1). Other aromatic AEDs including phenytoin and lamotrigine have also been investigated for cADR risk association with *HLA-B*15:02* (Figure 1). Whilst, phenytoin has been associated with SJS/TEN in the Han Chinese[24, 48], Thai[34] and Malaysian[50] populations, no significant association was found in two additional Thai studies[51, 52] (Table 1). There is also a lack of evidence linking lamotrigine-induced SJS/TEN to HLA-B*15:02 carriage in patients of Han Chinese descent[24, 27, 48] (Table 1). This absence of association is mainly attributed to small sample sizes in these reports, therefore larger cohort studies are needed to determine whether this HLA allele confers risk in lamotrigine-induced SJS/TEN.

AED-induced DRESS/HSS and HLA-B*15:02

To date there have been relatively few studies confirming the *HLA-B*15:02* risk association and AED-induced DRESS/HSS. Several reports of carbamazepine-induced DRESS have failed to identify risk association with *HLA-B*15:02* in European[29, 53], Han Chinese[23, 28], Vietnamese[40], Singaporean[45] and Malaysian[50] populations. However, a Thai study by Yampayon *et al.*[51] reported an inverse risk association for phenytoin-induced DRESS, with greater *HLA-B*15:02* frequencies represented in the drug tolerant controls compared to cases (Table 1). For phenytoin-induced DRESS/HSS there has only been a single report linking *HLA-B*15:02* in a Thai population[51], which contradicts the non-

significant findings of an alternate Thai study comparing DRESS cases to phenytoin-tolerant controls[52] (Table 1). Based on these small cohort studies, *HLA-B*15:02* allele does not appear to increase the risk of AED-induced DRESS/HSS.

AED-induced MPE and HLA-B*15:02

The milder cADR pathology of AED-induced MPE also does not appear to be linked with *HLA-B*15:02*. In a comprehensive genome wide association study (GWAS) by McCormack *et al.*[19], the authors did not report a significant association for carbamazepine-induced MPE with *HLA-B*15:02* in either European or Asian populations (Table 1). For both lamotrigine- and phenytoin-induced MPE the *HLA-B*15:02* frequency was not reported in either population[19]. Several alternate cohort studies also failed to demonstrate a *HLA-B*15:02* association with carbamazepine-induced MPE (Singaporean[45], Han Chinese[23, 26, 28, 31, 32], and Thai[34]). This finding also extended to other AEDs including oxcarbazepine (Han Chinese[54], Thai[49] and Taiwanese[49]), phenytoin (Thai[34]) and lamotrigine (Han Chinese[55] and Korean[56]) (Table 1).

Although the lack of an association may be due to small sample sizes in each cohort study, collectively they suggest that the *HLA-B*15:02* risk association is restricted to the more severe pathologies such as SJS/TEN. Thus *HLA-B*15:02* is not a universal marker for the entire spectrum of AED-induced cADRs.

AED-induced cADRs and HLA-A*31:01

Contrary to the relatively restricted association of *HLA-B*15:02* with the more severe forms of AED-induced cADR pathologies, *HLA-A*31:01* has been associated with mild, multi-organ/multi-system and severe cADRs. One of the earliest reports examining *HLA-A*31:01* risk association with carbamazepine-induced cADRs demonstrated significance in a pooled MPE/HSS patient cohort, as well as in MPE patients alone, but interestingly not for carbamazepine-induced HSS patients alone[23] (Table 1). In 2011, two independent GWAS publications established that the *HLA-A*31:01* allele was significantly associated with carbamazepine-induced cADRs. The Japanese GWAS study by Ozeki *et al*. (2011)[47] identified an increased risk of the *HLA-A*31:01* allele with a range of carbamazepine-induced cADRs (DRESS, SJS/TEN, MPE and other rashes including erythema multiforme and fixed drug reaction) (Table 1). The second GWAS study by McCormack *et al.* (2011)[53] also demonstrated increased risk of carbamazepine-induced MPE, DRESS and SJS/TEN in Europeans (Table 1). Corroborating these GWAS investigations, reports from Han Chinese (Taiwan)[29], European[19, 29], Canadian (mixed ethnicity)[44], Spanish Romani[42] and Korean[57] confirmed a strong *HLA-A*31:01* association with carbamazepine-induced DRESS and/or MPE, but not for SJS/TEN (Table 1).

It is important to note that studies with small case numbers may have been underpowered. The sample size required to detect association is strongly influenced by allele frequency and effect size[58]. The complexity of the pathways leading to a cutaneous reaction (*e.g.* one variant with large effect size, or involvement of multiple variants with small effect size and/or variants with a protective effect) may differ across cADR types. Consequently, pooling cases with differing phenotypes that share molecular underpinnings

would enhance the power to detect risk variants while pooling those with differing causal pathways would reduce study power. These factors and differing *HLA-A*31:01* population frequencies may explain, in part, the contradictory findings.

Currently, the *HLA-A*31:01* and AED-induced cADR association is limited to carbamazepine, as there are no significant GWAS reports of phenytoin-induced MPE in either European or Asian populations[19]. Given the current body of evidence it appears that *HLA-A*31:01* risk association traverses a range of carbamazepine-induced cADR pathologies across divergent ethnicities.

AED-induced cADRs and HLA-A*24:02

A third HLA class I allele, *HLA-A*24:02*, has also been associated with AED-induced cADRs that confers differing risk based on pathology severity and ancestry. Interestingly, studies examining *HLA-A*24:02* and lamotrigine-induced pathologies demonstrated statistically significant risk for SJS/TEN (Han Chinese[26, 33]), DRESS (Spanish Romani[42]) and MPE (Korean[56]) (Table 1). However, contrasting studies of lamotrigine-induced MPE failed to find an association with *HLA-A*24:02* in Han Chinese[26, 55] and European[19] populations (Table 1). Furthermore, for both carbamazepine- and phenytoin-induced cADRs there have been opposing reports of *HLA-A*24:02* risk. One study identified an association in a SJS/TEN cohort of Han Chinese descent (Southern China) for both carbamazepine and phenytoin[26] (Table 1). However, no *HLA-A*24:02* association with phenytoin-induced SJS/TEN was shown in a geographically distinct population of Han Chinese (Taiwan) descent[48], or for carbamazepine-induced SJS in a Korean

population[57]. Interestingly, an inverse association of carbamazepine-induced SJS/TEN and *HLA-A*24:02* was demonstrated in the Han Chinese population located within Taiwan[23] (Table 1). There was also no *HLA-A*24:02* association identified in a GWAS study of carbamazepine-induced cADRs in a Japanese population[47], which may have been influenced by the high *HLA-A*24:02* carrier frequency (Table 2). Again, based on these small cohort sizes and limited clinical reports it appears that the *HLA-A*24:02* allele could potentially increase risk, but larger studies are needed to confirm this association.

Extending the HLA risk to broad serotypes

In addition to *HLA-B*15:02*, there is some evidence of HLA risk association with AED-induced cADRs extending to other members of the broader HLA-B15 serotype, which vary in amino acid composition (selected alleles in Figure 2 show polymorphisms ranging from 1-7 amino acids). For instance, carbamazepine-induced SJS/TEN was associated with the HLA-B75 split, including *HLA-B*15:08* observed in a single homozygous patient[37], *HLA-B*15:11* in Japanese[46], Korean[57] and Han Chinese[26, 33] populations, and *HLA-B*15:21* in patients of Javanese/Sudanese[43] descent (Table 1). Two additional HLA alleles have been linked within the HLA-B15 serotype: *HLA-B*15:18* (HLA-B70 split) with carbamazepine-induced SJS/TEN in Japanese patients[59], and *HLA-B*15:13* (HLA-B77 split) with phenytoin-induced SJS/TEN and DRESS[50] (Table 1). However, the closely related HLA-B62 split, which includes the common *HLA-B*15:01*, does not confer risk[24, 50, 60, 61].

Beyond pharmacogenomics, functional studies have demonstrated carbamazepine-induced cytotoxic T lymphocyte (CTLs) can respond to a range of HLA-B75 family members (*i.e. B*15:02, B*15:08, B*15:11, B*15:21*), but not to HLA-B62 (*i.e. B*15:01*) or HLA-B72 (*i.e. B*15:03*) serotypes[62]. This data implicates three amino acid residues located within the peptide-binding cleft (Asn63 [shared by all B75 family members], Ile95, Leu156) being crucial for CTL activation. This evidence implies that all HLA-B75 family members, not just the prevalent *HLA-B*15:02*, confer risk in carbamazepine-induced cADRs. Therefore, the HLA genetic screening recommendations may need to be expanded to include the extended HLA-B75 family to further circumvent development of cADRs in at risk individuals.

Whilst there has been a case study purporting the presence of *HLA-A*31:01*-restricted carbamazepine-specific T cells in a patient with MPE[63], there are limited studies addressing the broader HLA-A19 serotypes (includes A29, A30, A31, A32, A33, A74; selected alleles shown in Figure 3) and AED-induced cADRs. More recently, in a study by Ramirez *et al.* (2017)[42] three of four carbamazepine-induced DRESS cases expressed a HLA-A19 serotype (*HLA-A*31:01*, *HLA-A*32:01* and *HLA-A*33:03*). Associations have also been identified between *HLA-A*33:03* and carbamazepine-induced DRESS[41], as well as for carbamazepine-induced SJS/TEN[25]. Finally, the HLA-A74 serotype has been shown to increase the risk of carbamazepine-induced SJS/TEN compared to a drug-naïve population[41]. However, these studies must be interpreted with caution given the small number of cases available for analyses (Table 1). Consequently, further investigation of HLA-A19 family members and AED-induced cADRs will be of interest to determine their ability to modulate risk.

Immunological mechanism of AED-induced cADRs

There are three prevailing mechanisms theorising how small molecule drugs elicit T cell-mediated hypersensitivity responses (reviewed in Illing *et al.* (2016)[64]); the hapten/prohapten concept (as hypothesised to occur in penicillin hypersensitivities)[65], pharmacological interaction with immune receptors (p-i) concept (thought to explain the mechanism of carbamazepine hypersensitivity)[66] and the altered peptide repertoire (observed for abacavir hypersensitivity)[67, 68].

The p-i mechanism of T cell stimulation is predicated on the non-covalent and labile interaction between the drug or a metabolite, the HLA-peptide complex[62] and the T cell receptor (TCR)[69]. These reactions are characterised by an absence of intracellular antigen processing[62] and minimal disruption of the self-peptide repertoire[70]. Most investigations dissecting the mechanism underpinning the p-i concept have involved either T cell lines or clones derived from patients exposed to carbamazepine[62, 71, 72], lamotrigine[73] and/or phenytoin[74]. These studies also revealed functional characteristics of AED-specific T cells, which included the expression of a range of proinflammatory (IFN³, IL-5, macrophage inflammatory protein [MIP]-1± and ², RANTES, I-309) and cytolytic (granulysin, perforin, granzyme B, FasL) molecules following re-exposure to the culprit drug.

A report from Ko *et al.* (2011)[75] also suggested that specific TCR subtypes may be required for drug recognition, defining a commonly expressed VA-22 and VB-11 TCR signature found in Taiwanese *HLA-B*15:02*+ patients with carbamazepine-induced severe bullous reactions[75]. Whilst, in a study of lamotrigine-induced cADRs there was a high

proportion of V² 5.1 expressed on T cells, suggesting that genetic variants within genes encoding the receptor might modify susceptibility[73]. Broader studies of TCR clonotypes across phenotype, ethnicity and HLA carriage are required to determine whether unique molecular signature(s) drive AED-induced cADRs, and whether these delineate pathology.

Cross-reactivity in AED-induced cADRs is common

Individuals who develop a cADR to one aromatic AED are often at risk of developing a cADR to related drugs that is independent of the HLA. The cross-reactivity towards different AEDs may be driven by both the patient's genetic predisposition and structural similarities of the drugs[76]. There have been several studies investigating the likelihood of a subsequent rash from any given antiepileptic medication. For instance, aromatic AEDs have shown an expansive degree of a secondary reaction to an alternate AED (range 13-80%[76-79]), with a heightened risk of subsequent rash in patients following secondary exposure to carbamazepine (Figure 4). This highly variable rate of AED cross-reactivity implies that there may be other genetic, immune-related factors or the effects of drug metabolism at play. For instance, studies have shown that an arene oxide metabolite produced from a minor metabolic pathway may be responsible for cross-reactivity[76-78]. This metabolite through covalent interactions could potentially bind to other molecules (*i.e.* the "hapten hypothesis") if not detoxified promptly due to a prolonged half-life[76-78]. However, due to the instability of arene oxide metabolites[80] this observation requires further validation. Finally, these studies corroborate the risk of cross-reactivity where a previous rash is a strong predictor (p-value <0.001) of a future aromatic AED-induced cADR.

Consequently, the mechanism of challenge with an alternate aromatic AED driving greater immunopathology mirrors the prototypical T cell-mediated immune response against recurrent infections with the same pathogen[81]. Considering the highly variable risk of aromatic AED cross-reactivity, a second non-aromatic AED, which is less likely to cause a cADR[82], could be prescribed as a safer alternative.

HLA linkage and AED-T cell cross-reactivity

Given the genomic risk factors contributing to cADR pathophysiology, it is possible that genetic variants also influence T cell cross-reactivity. For instance, there is a case report of *HLA-B*15:02*+ patients reacting to multiple aromatic AEDs (case 1: carbamazepine and oxcarbazepine, case 2: phenytoin, phenobarbital and carbamazepine)[83]. However, to date there has only been a single study investigating whether HLA genes contribute to subsequent cADRs following rechallenge with alternative AEDs to the initial causative drug. A total of 60 Chinese patients (Beijing, China) were recruited that had primary AED-induced cADRs (54 MPE, 6 SJS/TEN)[84]. The study found that the secondary rash can be milder or independent of the severity of the previous cADR, which may explain why the secondary reactions were all MPE[76, 77, 84]. The *HLA-B*15:02* allele was shown not to be significantly associated with T cell cross-reactivity. As previously stated, the *HLA-B*15:02* allele is not associated with the milder manifestation of MPE and thus the absence of positive association was not unexpected[84]. Interestingly, the *HLA-A*24:02* allele was indicative of lower risk for secondary AED-induced MPE[84], suggesting that these patients could receive an alternative aromatic AED. Given the small number of samples and evidence that *HLA-*

*A*24:02* associates with risk of a primary cADR, further prospective studies are needed to clarify the role of this allele in risk modification of both primary cADR and T cell cross-reactivity.

Furthermore, studies investigating AED cross-reactivity have demonstrated T cell lines/clones derived from patients with carbamazepine-induced cADRs can also recognise the metabolite carbamazepine-10,11-epoxide and other aromatic AEDs, including dihydro-carbamazepine, oxcarbazepine and eslicarbazepine acetate[62, 72].

HLA as a pharmacogenomic biomarker and FDA recommendations

In 2007 the US Food and Drug Administration (FDA) mandated regulatory recommendations for pre-treatment *HLA-B*15:02* genetic screening as a pharmacogenomic biomarker in individuals of Asian descent[85, 86]. These FDA recommendations have been adopted worldwide, resulting in safer use of the first-line antiepileptic medications[86]. Since release of the 2007 FDA recommendation there has been some investigation evaluating the effectiveness of this genetic screening policy in preventing cADR incidences, particularly for SJS/TEN in Han Chinese populations. Interestingly in a Hong Kong study, a change in clinical practice was noted which avoided pre-treatment genetic screening, with clinicians likely to prescribe an alternate AED to carbamazepine rather than request *HLA-B*15:02* screening. However, this change in prescribing practices did not alter the overall incidence of SJS/TEN as more cases from increased use of phenytoin in the post-policy period were reported. Thus, the cost benefits of reducing carbamazepine-induced SJS/TEN were mitigated by increased incidences of phenytoin-induced SJS/TEN[12]. Conversely, a separate

Hong Kong study demonstrated that the screening policy if implemented as per the guidelines was indeed cost effective and as efficient as other routine clinical procedures (including mammography and PAP smear testing) to prevent death[87]. The authors did qualify that the cost of point-of-care *HLA-B*15:02* genetic screening would need to be less than USD$37 in order to improve efficiency as prevention of one carbamazepine-induced SJS/TEN case or death required screening of either 442 or between 1,474-8,840 individuals, respectively. Consequently, without an effective screening strategy some individuals could miss out on an efficacious treatment, limiting the cost effectiveness of the screening program.

At present there is no mandated FDA recommendation for *HLA-A*31:01* genetic screening, although the FDA-approved label for carbamazepine does note the moderate association of this allele and the risk of developing hypersensitivity reactions[85]. The predicted cost effective benefits of *HLA-A*31:01* screening suggest a need to test between 47-67 individuals of either Caucasian or Japanese descent to avoid a single cADR case[88], and testing has resulted in a 40% decreased incidence of carbamazepine-induced cADRs in the latter population[89]. Given the rising incidence of reported *HLA-A*31:01*-related AED-induced cADRs there is accumulating evidence to support pre-treatment genetic screening in at risk populations.

Statistical evaluation of HLA associations

Despite the pharmacogenomic biomarkers *HLA-B*15:02* and *HLA-A*31:01* having strong associations with the more severe or mild to severe AED-cADRs respectively, alone they are

not 100% predictive (Table 1). There are two ways to quantify the quality of a diagnostic test that include: (1) specificity/sensitivity (proportion of true positive and negative outcomes)[90] and (2) positive predictive value (PPV)/negative predictive value (NPV; differs from specificity/sensitivity by utilising the prevalence of the disease)[91]. Therefore, the predictive values can be variable depending on the prevalence of the disease and suggests whether or not to screen individuals of that population[92]. Both measures are important in interpreting diagnostic results when ruling out/in a particular diagnosis as well as effective treatment options.

Based on the significant HLA association studies collated in Table 1, only 35.4% reported specificity/sensitivity and 26.2% calculated PPV/NPV. The main outcomes from these collective statistical analyses imply that; if a person of Han Chinese descent does not express *HLA-B*15:02* then the chances of developing severe bullous reactions (*i.e.* SJS/TEN) is extremely unlikely (100% prediction), but if a person is *HLA-B*15:02* positive there is a degree of unpredictability (PPV range: 0.73-100%; sensitivity range: 22.2-100%) as to whether they will develop AED-induced SJS/TEN. For *HLA-A*31:01* risk association a similar trend was observed, with only a minority of *HLA-A*31:01* positive individuals (PPV range: 0.59-12.7%; sensitivity range: 50-70%) developing AED-induced cADRs (Table 1). The low PPVs are not unexpected since the prevalence of DRESS and SJS/TEN occur in low frequencies (from 0.001-0.025%)[10-12] in at risk populations. Consequently, these data suggest that there may be other unaccounted gene variants, epigenetic or environmental contributing factors influencing risk.

Given that the PPVs are relatively low, a patient expressing either the *HLA-B*15:02* or *HLA-A*31:01* allele may unnecessarily be excluded from potentially efficacious clinical intervention, and currently 30% of patients have drug resistant epilepsy[93] further complicating treatment options. Consequently, there is a critical need to unveil additional and/or more robust biomarkers to improve genetic screening tests for AED-induced cADRs.

Limitations of identifying genomic risk variants

Since the discovery of *HLA-B*15:02* and carbamazepine-induced SJS/TEN[22], there have been few additional genetic risk markers for AED-induced cADRs identified. These include *HLA-A*31:01*[19, 47, 53], *CFHR4*[19], *EPHX1*[94] and *CYP2C*9*[17]. For many existing studies, findings must be interpreted with caution due to small cohort sizes (range: 1-132 cases; 0-869 drug tolerant controls; 0-8,862 healthy controls; Table 1) and it is likely that other genetic factors are in play that remain to be elucidated.

Genetic association studies have proven utility for identifying genetic risk factors for Mendelian-like disorders, whereby a single marker of large effect is causal. Complex disease models that might involve multiple genetic variants of small effect sizes, protective variants, non-coding and rare variants provide greater challenge[95]. For instance, genetic variations with small effect size but important biological consequence can remain elusive under commonly applied stringent statistical cut-offs (*i.e.* 5e-8 for GWAS significance)[95].

With reducing cost, whole genome sequencing (WGS) is increasingly viable for research and clinical investigations. WGS overcomes the limitations of whole exome and common single nucleotide polymorphisms array technologies[96] and will enhance

opportunity to elucidate risk markers for cADRs. Importantly, to advance our understanding of the disease pathology it will be necessary to draw information from multiple sources, including biological pathways.

Gene expression perturbations driving immunopathology

Differential gene expression data (*i.e.* transcriptomics) has the potential to reveal important biological pathways and novel variants in addition to the single nucleotide polymorphisms originally identified from GWAS[97]. There are a wide variety of technologies to interrogate RNA information, with RNA-Sequencing (RNA-Seq) being the current gold standard[98]. This technology also has the capability of measuring transcriptomic changes at a single cell level, excluding noise associated with bulk cell populations, to provide information associated with specific cellular subpopulations (*e.g.* T cells)[99].

At present, there has been limited investigation of differential gene expression in drug-induced cADRs. In a study by Chung *et al.* (2008)[100], transcriptomic alterations in cell death pathways of peripheral mononuclear cells (PBMCs) and cellular components of blister fluid from five SJS/TEN patients were explored using microarrays. Whilst SJS/TEN keratinocyte apoptosis was previously reported to be mediated either by Fas-FasL interactions[101] or via granzyme B/perforin cytolysis[102], this study revealed that granulysin was the key molecule precipitating keratinocyte cell death. An alternate microarray study[103], examined paired PBMC gene expression differences between the acute and resolved phases of cADRs (including MPE, DRESS, SJS/TEN) in 13 patients.

From 12,000 genes, only nine immune-related genes (*PF4V1*, *MMP9*, *PLA2G2D*, *CFB*, *IL17A*, *PTPN9*, *FGC*, *PLA2G5*, *IFNW1*) were upregulated during the acute phase.

These studies have demonstrated the potential of transcriptomics to highlight key factors in complex disease pathology and future analyses capitalising on the greater scope of RNA-Seq (>30,000 transcripts)[104] may offer insights into key risk genes within biological pathways that could be used as susceptibility markers across the disease spectrum.

Concluding remarks

The economic cost of ADR associated hospitalisations is a considerable burden on global healthcare systems. Strategies to identify novel associated risk factors are needed to not only decrease incidence rates and prevent episodes of morbidity and mortality, but also empower clinicians to better manage patient treatment (*i.e.* precision medicine). Pharmacogenomic studies have been pivotal in the identification of strong genetic risk associations between specific HLA class I alleles (*HLA-B*15:02*, *HLA-A*31:01* and *HLA-A*24:02*) and a range of AED-induced cADRs. Indeed, the FDA recommendation of AED pre-treatment genetic screening for *HLA-B*15:02* in individuals of Asian descent led to a world-wide decreased incidence of carbamazepine-induced SJS/TEN. There is also evidence to suggest *HLA-A*31:01* genetic screening would be both cost effective and reduce disease burden. The concerning aspect of pre-treatment screening programs is that the HLA risk variants identified thus far are neither necessary nor sufficient (<5% PPV), thereby eliminating these individuals from otherwise efficacious treatment. Clearly, there is an immediate unmet

clinical need to improve the predictability of AED-induced cADRs using novel biomarkers that extend beyond the *HLA* alleles.

The spectrum of cutaneous pathologies is complex, suggesting there may be combinations of modifying gene variants that collectively impact on immunopathological pathways. The utility of transcriptomics to identify dysregulated genes and associated pathways in the setting of complex disease pathologies could enable a more informed interrogation of genomic datasets. These approaches may elucidate markers that act concurrently or independently of HLA class I carrier status of patients. Biomarkers with predictive capacity will facilitate pre-treatment screening for patients at risk of AED-induced cADRs and improved understanding of the molecular mechanisms that will inform diagnosis and clinical management of these potentially fatal reactions.

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Table 1: HLA-associations of AED-induced cADRs

AED	Categorisation/ indication	cADR	HLA	Ethnicity	OR or *Relative Risk**	No. cases, drug-tolerant, healthy Controls (# with allele)	P-value	PPV/NPV (%)	Sensitivity/ Specificity (%)	[Ref]
Carbamazepine	Anticonvulsant/ epilepsy, bipolar disorder	SJS/TEN	B*15:02	Han Chinese	2,504^ & 895§	44(44), 101(3), 93(8)	3.13e-27^ & 1.38e-21§	93.6/100	100/97	[22]
					1,357^	60(59), 144(6), 0	1.60e-41^	-	-	[23]
					89.25^	26(24), 135(16), 0	3.51e-18^	-	92.3/88.1	[24]
					18.2^	35(8), 125(2), 0	<0.001^	-	-	[25]
					12.37^	56(39), 179(28), 0	5.63e-15^	-	69.6/84.4	[26]
					36.0^	16(12), 39(3), 0	<0.001^	-	-	[27]
					97.62^	112(99), 152(11), 0	5.80e-43^	90/92	88/93	[28]
					58.1^ & 37.0§	53(41), 72(4), 710(60)	<0.001^ & <0.001§	3.37/99.94	77.4/94	[29]
					152^ & 158§	17(16), 21(2), 185(17)	<0.0001^ & <0.0001§	-	-	[30]
					184^ & 173.3§	8(8), 50(4), 71(6)	<0.05^ & <0.05§	-	-	[31]
					114.8^ & 85.1§	9(9), 80(11), 62(11)	<0.001^ & <0.001§	45/100	100/86.25	[32]
					17.55^ & 21.58§	18(13), 93(12), 93(10)	<0.001^ & <0.001§	-	72.2/87.1	[33]
				Thai	25.5^	6(6), 42(8), 0	0.0005^	43/100	100/75	[34]
					54.76^	42(37), 42(5), 0	2.89e-12^	1.92/99.96	88.1/88.1	[35]
					75.4^	34(32), 40(7), 0	<0.001^	1.43/99.98	94.1/82.7	[36]

				Indian	71.4^	8(6),10(0), 0	0.0014^	-	-	[37]
					-^	9(2), 37(0), 0	0.035^	100/84.1	22.2/100	[38]
					33.33^	7(4), 52(2), 0	1.05e-3^	-	57.1/96.2	[39]
				Vietnamese	33.78^	35(32), 25(6), 0	< 0.0001^	84.2/86.4	91.4/76.0	[40]
				Malaysian	16.15§	16(12), 0, 300(47)	7.87e-6§	-	-	[41]
				Spanish Romani	47.00^ & 507.00§	2(1), 23(0), 253(0)	0.017^ & <0.001§	-	-	[42]
				Javanese & Sudanese	6.5^ & 6.78§	12(8), 17(4), 236(54)	0.029^ & 0.0021§	-	-	[43]
				Canadian (mixed ethnicity)	38.65^	9(3), 87(1), 0	0.0022^	-	-	[44]
				Singaporean	27.2^	5(5), 10(1), 0	-^	-	-	[45]
				European	-^ & -§	20(0), 43(0), 8862(4)	NS^ & NS§	-	-	[29]
				Japanese	-^	61(0), 376(-), -	NS^	-	-	[47]
					-§	14(0), -, 493(-)	-§	-	-	[46]
				Korean	23.3^	7(1), 50(0), 0	NS^	-	-	[57]
			B*15:11	Han Chinese	30.77^	56(4), 179(0), 0	0.003^	-	-	[26]
					31.0§	36(2)•, 0, 528(1)•	0.01§	-	-	[33]
				Japanese	16.3§	14(4), 0, 493(5)	0.0004§	-	-	[46]
				Korean	18.0^	7(3), 50(2), 0	0.011^	-	-	[57]
			B*15:18	Japanese	*13.58**§	10(1)•, 0, 493(5)	-§	-	-	[59]
			B75	Javanese and Sudanese	12.00^ & 8.56§ (B*15:02 and B*15:21)	12(10), 17(5), 236(87)	0.0078^ & 0.0018§	-	-	[43]

			A*24:02	Han Chinese	0.26^	60(5), 144(41), 0	0.026^	-	-	[23]
					2.33^	56(17), 178(28), 0	0.015^	-	30.4/84.3	[26]
					3.18^ & 2.34§	32(10)•, 64(8)•, 528(86)•	0.03^ & 0.03§	-	-	[33]
				Korean	0.5^	7(2), 50(21), 0	NS^	-	-	[57]
			A*31:01	European	25.93^	12(5), 257(10), 0	8e-5^	-	-	[53]
					-^ & -§	20(3), 257(10), 8862(396)	NS^ & NS§	-	-	[29]
				Han Chinese	0.59^	60(1), 144(6), 0	NS^	-	-	[23]
					-^ & -§	53(1), 72(3), 710(26)	NS^ & NS§	-	-	[29]
				Canadian (mixed ethnicity)	1.33^	9(0), 91(3), 0	1.000^	-	-	[44]
				Japanese	33.9^	6(5), 420(54), 0	2.35e-4^	12.7/98.7	-	[47]
			A*33:03	Han Chinese	12.9^	20(7), 125(5), 0	<0.001^	-	-	[25]
			A74	Asian (mixed ethnicity)	13.62§	16(3), 0, 300(5)	0.0408§	-	-	[41]
		HSS/ DRESS	B*15:02	Han Chinese	0.79^	13(0), 144(6), 0	NS^	-	-	[23]
					0.26^	23(0), 152(11), 0	NS^	0/86	0/93	[28]
					-^ & -§	10(0), 72(4), 710(60)	NS^ & NS§	-	-	[29]
				European	-^ & -§	10(0), 43(0), 8862(4)	NS^ & NS§	-	-	[29]
				Vietnamese	6.33^	3(2), 25(6), 0	0.159^	-	-	[40]
				Singaporean (mixed ethnicity)	1.67^	6(0), 10(1), 0	-^	-	-	[45]

			A*31:01	Han Chinese	12.9^	23(7), 152(5), 0	2.4e-3^	-	-	[28]
					23.0^ & 26.3§	10(5), 72(3), 710(26)	<0.001^ & <0.001§	0.59/99.97	50/95.8	[29]
					6.36^	13(2), 144(4), 0	NS^	-	-	[23]
				European	57.6^ & 49.9§	10(7), 257(10), 8862(396)	<0.001^ & <0.001§	0.89/99.98	70/96.1	[29]
					12.41^	27(10), 257(10), 0	0.030^	-	-	[53]
				Spanish Romani	22.00^ & 35.14§	4(2), 23(1), 253(7)	0.047^ & 0.006§	-	-	[42]
				Canadian (mixed ethnicity)	26.36^	6(3), 91(3), 0	0.0025^	-	-	[44]
				Japanese	9.5^	36(21), 420(54), 0	2.06e-9^	12.7/98.7	-	[47]
				Korean	8.8^	17(10), 50(7), 0	0.001^	-	-	[57]
			A*33:03	Spanish Romani	20.14^ [52.71‡], 41.83§	4(1), 23(0)[61(0)‡], 253(2)	0.111^ [0.009‡] & 0.046§	-	-	[41]
		MPE/ HSS	A*31:01	Han Chinese	12.17^	31(8), 144(4), 0	0.0021^	-	-	[23]
		MPE	B*15:02	Han Chinese	0.6^	22(2), 187(25), 0	0.53^	-	-	[19]
					1.35^	18(1), 144(6), 0	NS^	-	-	[23]
					0.91^	132(19), 179(28), 0	0.76^	-	-	[26]
					0.8^	51(4), 152(11), 0	NS^	-	-	[28]
					1.4^ & 1.3§	28(3), 50(4), 71(6)	0.697^ & 0.724§	-	-	[31]
					2.16^ & 1.60§	39(10), 80(11), 62(11)	0.110^ &	27/75	8/93	[32]

							0.341[§]			
					-[^] & -[§]	80(4)[•], 104(5)[•], 144(6)[•]	1.000[^] & 0.748[§]	-	-	[55]
				European	-[^]	95(0), 869(0), 0	-[^]	-	-	[19]
				Thai	1.21[^]	5(0), 50(8), 0	1.14[^]	-	-	[34]
				Canadian (mixed ethnicity)	1.09[^]	26(0), 91(1), 0	1.00[^]	-	-	[44]
				Singaporean (mixed ethnicity)	0.90[^]	11(1), 10(1), 0	-[^]	-	-	[45]
			A*31:01	Han Chinese	17.5[^]	18(6), 144(4), 0	2.20e-3[^]	-	-	[23]
					0.81[^]	22(1), 166(1), 0	0.81[^]	-	-	[19]
					4.68[^] (Taiwan)	51(7), 152(5), 0	NS[^]	-	-	[28]
				European	5.5[^]	95(16), 868(27), 0	1.47e-10[^]	-	-	[19]
					8.33[^]	106(23), 257(10), 0	8.00e-7[^]	-	-	[53]
				Canadian (mixed ethnicity)	8.57[^]	26(6), 91(3), 0	0.0037[^]	-	-	[44]
			A*24:02	Han Chinese	1.26[^] (Taiwan)	18(6), 144(41)	NS[^]	-	-	[23]
					1.73[^]	131(32), 178(28), 0	0.056[^]	-	-	[26]
					-[^] & -[§]	80(16)[•], 104(14)[•], 144(27)[•]	0.234[^] & 0.820[§]	-	-	[55]
		cADR	A*24:02	Japanese	-[^]	61(37), 376(211), 0	0.58[^]	-	-	[47]
Oxcarbazepine	Anticonvulsant/ epilepsy	SJS/TEN	B*15:02	Han Chinese	80.7[§]	3(3), 0, 93(7)	8.40e-4[§]	-	-	[48]
				Taiwanese	27.9[^]	17(12), 101(8), 0	1.12e-9[^]	0.73/99.97	70.6/92.1	[49]

				Thai	49.0^	3(3), 99(12), 0	2.65e-3^	-	100/87.9	[49]
		MPE	B*15:02	Han Chinese	1.23^ & 0.46§	28(1)•, 70(2)•, 528(39)•	1.00^ & 0.699§	-	-	[54]
				Taiwanese	0.58^	21(1), 101(8), 0	1.00^	-	-	[49]
				Thai	21.00^	1(1), 99(2), 0	0.13^	-	-	[49]
Phenytoin	Anticonvulsant/ epilepsy, seizures, anti-arrhythmic, muscle relaxant	SJS/TEN	B*15:02	Han Chinese	3.5^	15(7), 75(15), 0	0.045^	-	46.7/80	[24]
					5.1^ & -§	26(8), 113(9), 93(7)	0.0041^ & -§	-	-	[48]
				Thai	18.5^	4(4), 45(8), 0	0.005^	33/100	100/82	[34]
					2.28^ & 3.01§	15(5), 100(18), 758(108)	0.177^ & 0.0544§	-	-	[51]
					0.89^	39(5), 92(13), 0	NS^	-	-	[52]
				Malaysian	5.71^ & 8.61§	13(8), 32(7), 300(47)	0.016^ & 3.60e-4§	-	-	[50]
			B*15:13	Malaysian	11.28^ & 8.56§	13(7), 32(3), 300(36)	0.003^ & 5.20e-4§	-	53.8/90.6	[50]
			A*24:02	Han Chinese	6.00^	13(6), 40(5), 0	0.027^	-	46.2/87.5	[26]
				Han Chinese (Taiwan)	0.5^	26(5), 113(37), 0	0.238^	-	-	[48]
		DRESS	B*15:02	Thai	0.1^ & 0.14§	21(0), 100(18), 758(108)	0.0402^ & 0.0995§	-	-	[51]
					0.64^	21(2), 92(13), 0	NS^	-	-	[52]
				Malaysian	-^ & -§	3(0), 32(7), 0	NS^ & NS§	-	-	[50]
			B*15:13	Malaysian	59.00^ & 50.73§	3(3), 32(3), 300(36)	0.003^ & 0.002§	-	-	[50]
		MPE	B*15:02	Thai	1.54^	9(1), 50(8), 0	0.84^	-	-	[34]

Lamotrigine	Anticonvulsant/ epilepsy, bipolar disorder	SJS/TEN	B*15:02	Han Chinese	3.25^	6(2), 30(4), 0	0.256^	-	-	[24]
					4.80^	7(2), 13(1), 0	0.212^	-	-	[27]
					5.1^ & -§	6(2), 67(6), 93(8)	0.127^ & -§	-	-	[48]
			A*24:02	Han Chinese	4.48^	22(10), 102(16), 0	0.005^	-	45.4/84.3	[26]
		DRESS	A*24:02	Spanish Romani	49.00^ & 34.53§	3(3), 10(1), 253(44)	0.015^ & 0.002§	-	-	[42]
		MPE	B*15:02	Han Chinese	-^ & -§	86(2)•, 88(4)•, 144(6)•	0.682^ & 0.713§	-	-	[55]
					0.8^	58(9), 102(19), 0	0.619^	-	-	[26]
				Korean	-^ & -§	21(0), 29(1), 485(2)	1.000^ & 1.000§	-	-	[56]
			A*24:02	Korean	4.09^ & 3.95§	21(15), 29(12), 485(188)	0.025^ & 0.005§	-	-	[56]
				Han Chinese	1.66^	55(13), 102(16), 0	0.221^	-	-	[26]
					-^ & -§	86(14)•, 88(18)•, 144(27)•	0.477^ & 0.636§	-	-	[55]
				European	0.9^	118(16), 811(130)	0.71^	-	-	[19]

DRESS: drug rash with eosinophilia and systemic symptoms; SJS/TEN: Stevens-Johnson syndrome and toxic epidermal necrolysis; MPE: maculopapular exanthema; OR: Odds Ratio; PPV: positive predictive value, NPV: negative predictive value

^ Compared to drug-tolerant controls

§ Compared to healthy controls/general population

[‡] Compared to all AED-drug tolerant controls

Calculated for all cADRs

• represents 2n diplotype

NS: non-significant with p-value >0.05

- no value reported

e is the exponential notation of $x10^{x}$ (*i.e.* 5.20e-4 is the same as $5.2\ x10^{-4}$)

Table 2: Global population carrier frequencies for HLA class I risk alleles

Ethnicity (Country/Continent)	**A*24:02 (n)**	**A*31:01 (n)**	**B*15:02 (n)**
Han Chinese (China)	0.1488 (6,425)	0.0299 (5,153)	0.0607 (7,884)
Han Chinese (Taiwan)	0.1580 (504)	0.0280 (504)	0.0450 (504)
Taiwanese (Taiwan)	0.2939 (2,746)	0.0135 (2,746)	0.0404 (2,746)
Caucasians (Europe)	0.0998 (105,125)	0.0262 (128,097)	0.0002 (87,922)
Japanese (Japan)	0.3642 (20,303)	0.0843 (20,303)	0.0004 (19,993)
Thai (Thailand)	0.0390 (142)	0.0181 (608)	0.0846 (591)
Indian (India)	0.1418 (3,582)	0.0411 (3,234)	0.0182 (3,081)
Korean (South Korea)	0.2205 (4,613)	0.0559 (4,613)	0.0146 (11,709)

Sample allele frequencies were calculated on the combined number of individuals in each population and then divided by the total count collected from www.allelefrequencies.net that was published by Gonzalez-Galarza *et al.* (2015)[105]

Figure Legends:

Figure 1: *Chemical structures of commonly prescribed aromatic antiepileptic drugs.*

Figure 2: *Polymorphisms of selected members within HLA-B15 serotype associated with AED-induced cADRs.*

Ribbon diagrams depicting the ±1 and ±2 helices and ² -sheet of the peptide binding cleft (residues 1-180) in selected members of the HLA-B15 serotype compared to *HLA-B*15:02:01:01* (polymorphic amino acid (AA) residues shown as red spheres). Molecular structures were generated using the RCSB Protein Data Bank file (PBD) 1XR8 (HLA-B*15:01)[106] and PyMol software (version 4.5). HLA allele sequences were aligned using IMGT/HLA Database[107, 108].

Figure 3: *Polymorphisms of HLA-A19 serotype members.*

Ribbon diagrams depicting the ±1 and ±2 helices and ² -sheet of the peptide binding cleft (residues 1-180) in selected members of the HLA-A19 serotype compared to *HLA-A*31:01:02:01* (polymorphic amino acid (AA) residues shown as red spheres). Molecular structures were generated using the RCSB PDB file IS9W[109] and PyMol software (version 4.5). HLA allele sequences were aligned using IMGT/HLA Database[107, 108].

Figure 4: *Cross-reactivity matrix of commonly prescribed aromatic AED-induced cADRs.*

Percentage of individuals who had a primary AED-induced cADR (left column) that reacted to a second prescribed AED-induced cADR (top row). Data extracted from four independent

studies: [#]Hirsch *et al. (*2008)[78], ^Wang *et al. (*2010)[76], *Alvestad *et al.* (2008)[77], [§]Hyson and Sadler (1997)[79].

Acknowledgements:

KM is supported by an Australian Government Research Training Program (RTP). AWP is supported by a National Health and Medical Research Council (NHMRC) Principal Research Fellowship. This work was supported by NHMRC project grant 1122099 to AWP. PK is supported by the Medical Research Future Fund Practitioner Fellowship. This work is partly supported by NHMRC project grant 1103979 to PK.

Biosketch:

Kerry Mullan is a PhD student in the Biomedicine Discovery Institute and Department of Biochemistry and Molecular Biology, Monash University. She holds a B.Biomed.Sc/B.Sc degree from Monash University and a M. Pharm from the University of Western Australia. In 2017, she completed an honours degree in pharmacogenomics from the University of Melbourne (via Royal Melbourne Hospital), where she investigated whole genome sequences and relatedness of AED-induced SJS/TEN. Her PhD utilises a multi-omics approach (genome, transcriptome and proteome) to identify key biomarkers conferring risk across the spectrum of AED-induced cADRs.

Dr Anderson, PhD, is a bioinformatician at the Department of Neuroscience, Monash University. Her PhD was awarded by the University of Western Australia and focussed on using transcriptomic data to investigate perturbation of the epigenome following *in utero* exposure to endocrine disruptors. Her current pharmacogenomics research aims to identify genetic biomarkers that modify susceptibility to adverse effects of anticonvulsant drugs, with a particular focus on cutaneous reactions, and birth defects and developmental delay in children exposed *in utero*.

Dr Patricia Illing, PhD, is a Research Fellow in the Department of Biochemistry and Molecular Biology and the Biomedicine Discovery Institute at Monash University. Her PhD, awarded by the University of Melbourne, focussed on the mechanisms underlying abacavir hypersensitivity syndrome and the association with HLA-B*57:01. Her current research encompasses epitope discovery in both adverse drug reactions and infectious disease.

Patrick Kwan, FRACP, PhD, is Professor of Neurology at Department of Neuroscience, Monash University. He is also a board-certified neurologist and Head of Epilepsy at the Royal Melbourne Hospital and Alfred Hospital. He graduated in clinical medicine from the University of Cambridge and obtained PhD from the University of Glasgow, UK. He is an elected Fellow of the Australian Academy of Health and Medical Sciences (FAHMS). His research interests include the outcomes of epilepsy and clinical pharmacology and pharmacogenomics of antiepileptic drugs.

Prof Anthony Purcell, PhD, is Deputy Head of Department and a NHMRC Principle Research Fellow in the Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute at Monash University. His research focuses on the identification of novel targets of immunity using immunoproteomics and associated technologies.

Dr Nicole Mifsud, PhD, is a Group Leader in Clinical Immunology in the Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute at Monash University. Her research expertise encompasses HLA immunology and immunogenetics, transplantation immunology, viral immunology and T cell biology. She was awarded her PhD from the University of Melbourne with her studies focussing on assessing the allogeneic T cell response in transplantation. Her current research explores inappropriate T cell responses and TCR cross-reactivity across a spectrum of immunological disorders including autoimmunity, drug allergy (i.e. T cell-mediated cADRs) and allograft rejection in solid organ transplantation.

Figure 1:

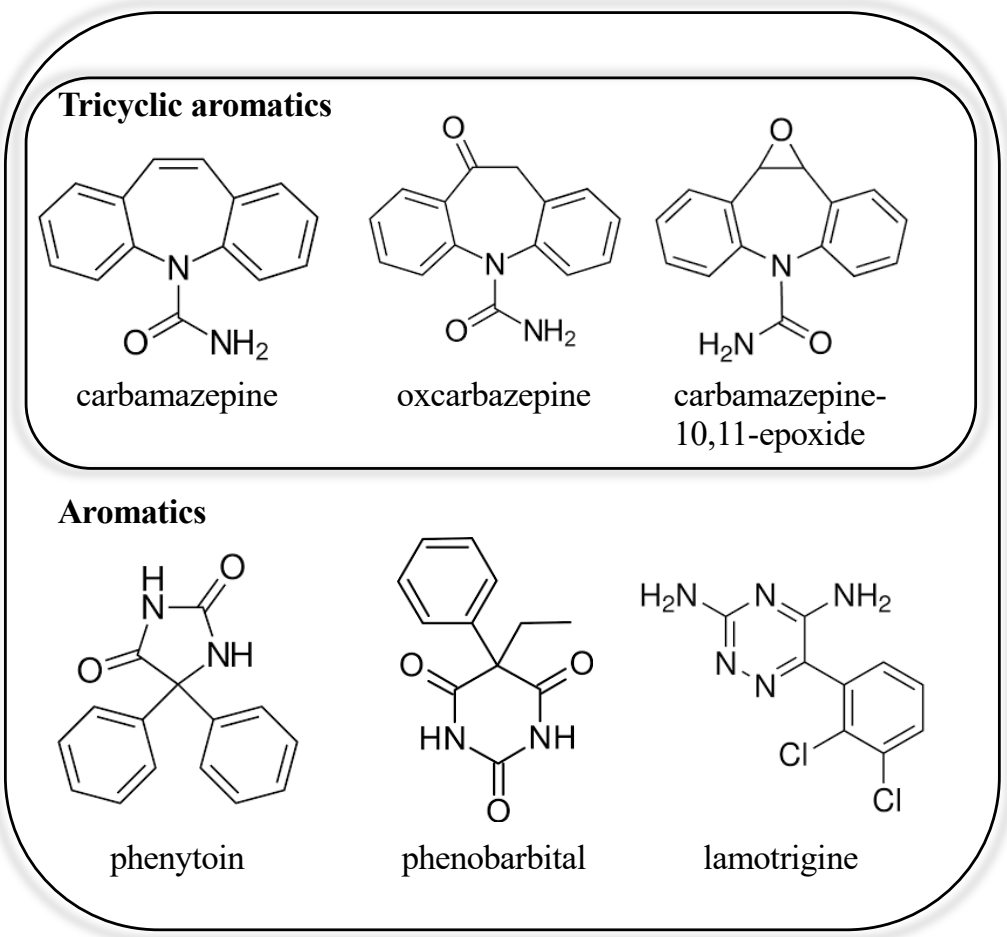
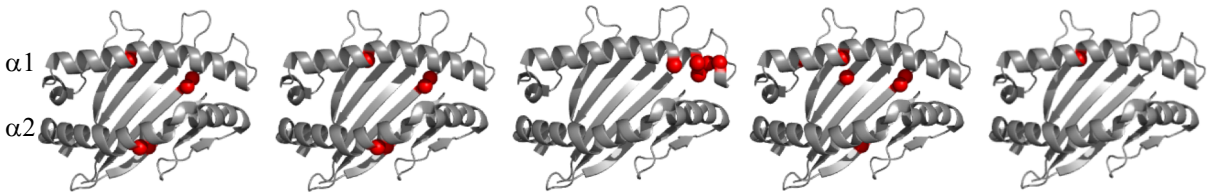
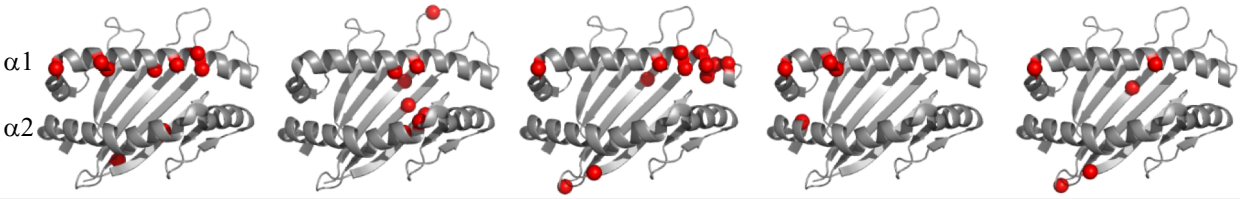


Figure 2:



	B*15:08	B*15:11	B*15:13	B*15:18	B*15:21
B15 split	B75	B75	B77	B70/71	B75
AA changes from B*15:02:01:01	5	5	5	7	1
Positions	S67F, I94T, I95L, Y113H, L156W	S67Y, I94T, I95L, Y113H, L156W	S77N, N80I, L81A, R82L, G83R	A24S, M45E, A46E, S67C, I94T, I95L, Y113H	S67C

Figure 3:



	A*29:01	A*30:01	A*32:01	A*33:01	A*74:01
AA changes from A*31:01:02:01	10	20	14	5	7
Positions	R56G, Q62L, E63Q, H70Q, I73T, V76A, D77N, D102H, Q114R, R184A	T9S, R17S, H70Q, I73T, M97I, Q114E, D116H, V152W, A193P, V194I, S207G, S246A, Q253E, P276L, P294L, F298I, A299T, R307M, S321T, M334V	T9F, R56G, I73T, V76E, D77S, G79R, T80I, L81A, R82L, G83R, S105P, F109L, P184A, V297M	R56G, Q62R, E63N, Y171H, K186R	T9F, R56G, I73T, S105P, F109L, P184A, V297M

Figure 4:

	cADR to 2nd AED (%)			
cADR to 1st AED (%)	carbamazepine	oxcarbazepine	phenytoin	lamotrigine
carbamazepine		33.0# 66.7^ 29.0*	57.6# 52.9^ 30.0* 40.0§	20.0# 29.4^ 13.0*
oxcarbazepine	71.4# 40.0^ 78.0*		33.3# 16.7^ 80.0*	37.5# 33.3^ 40.0*
phenytoin	42.0# 69.2^ 44.0* 58.0§	21.4# 25.0^ 50.0*		18.9# 20.0^ 27.0*
lamotrigine	26.3# 50.0^ 24.0*	20.0# 25.0^ 22.0*	38.9# 14.3^ 27.0*	