**Genetic predisposition to anticonvulsant hypersensitivity**

**Munir Pirmohamed**

MRC Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool, The Royal Liverpool and Broadgreen University Hospitals NHS Trust, and Liverpool Health Partners, Liverpool, UK.

**ORCID Number**: 0000-0002-7534-7266

**Author for correspondence**: Professor Sir Munir Pirmohamed,MRC Centre for Drug Safety Science, Department of Molecular and Clinical Pharmacology, University of Liverpool, Block A: Waterhouse Building, 1-5 Brownlow Street, Liverpool, UK, L69 3GL

Tel +44 151 794 5549
Fax +44 151 794 5059
Email munirp@liverpool.ac.uk

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**Introduction**

Anticonvulsant hypersensitivity is an important clinical problem where there is increasing evidence of genetic predisposition. This has been most evident with carbamazepine where two HLA alleles, *HLA-B\*15:02* and *HLA-A\*31:01*, have been identified. However, implementation remains sub-optimal even when test costs are reimbursed. This article describes recent advances in genetic predisposition to anticonvulsant hypersensitivity, in both the HLA and non-HLA regions, and highlights domains where further research is required.

**Background**

Epilepsy affects about 1% of the population. Most patients can be effectively treated with one or more anticonvulsant, although 20-30% remain refractory to treatment. A variety of drugs, of varying ages, are available for treatment. The overall risk-benefit ratio of these drugs is positive, but all of them can cause serious immune-mediated adverse drug reactions, which collectively are termed hypersensitivity reactions (figure 1).

Hypersensitivity reactions to anticonvulsants can have a variety of clinical manifestations ranging from mild maculopapular exanthema to more serious reactions such as DRESS (drug reaction with eosinophilia and systemic symptoms) and Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). DRESS, SJS and TEN are associated with significant mortality (~30% with TEN). A recent analysis of the FDA Adverse Event Reporting System showed that anticonvulsants had more reports of SJS/TEN than any other drug class (1), with the highest reporting odds ratios (ROR) for zonisamide (ROR 70.2), rufinamide (ROR 60), clorazepate (ROR 56), lamotrigine (ROR 53), phenytoin (ROR 26.3) and carbamazepine (ROR 24.5). Conventional epidemiological studies have also highlighted the risk of SJS/TEN, particularly with the older aromatic anticonvulsants, with the absolute risks per 100,000 exposed being 45.86 cases for phenytoin, 44.17 for lamotrigine and 20.38 for carbamazepine (2). The higher reported odds ratios with the newer anticonvulsants in studies utilising spontaneous adverse drug reporting (ADR) databases may reflect the Weber effect, where ADR reporting tends to decline after 2 years on the market.

**HLA and drug hypersensitivity**

There has been increasing interest in identifying genetic predisposing factors for anticonvulsant hypersensitivity, but this has focused largely on the older drugs. The most striking findings have been with specific HLA alleles. For carbamazepine (CBZ), *HLA-B\*15:02* was identified as a predisposing factor for CBZ-induced SJS/TEN in Han Chinese patients (3), and has now been replicated in other SE Asian populations. The strength of the predisposition, together with identification in a cohort study that prospective genotyping reduced the incidence of SJS/TEN, has led to the recommendation in drug labels that *HLA-B\*15:02* screening should be undertaken prior to the use of carbamazepine in South-East Asian populations. In Taiwan, after screening was introduced, cases of CBZ-induced SJS/TEN have declined by 87% over a 10-year period, but this is not all due to the use of *HLA-B\*15:02* testing since the use of CBZ also decreased by 83% over the same time period (4). Indeed only 25% of new users were screened before given CBZ, highlighting that implementation is far from perfect. This is also reflected in a study from Hong Kong where the availability of a genetic test for *HLA-B\*15:02* drove clinicians away from the use of CBZ to other drugs which were also associated with SJS/TEN, such that the total incidence of anticonvulsant-induced SJS/TEN remained stable despite a decrease in CBZ-induced SJS/TEN (5).

Although *HLA-B\*15:02* is the most important allele predisposing to CBZ-induced SJS/TEN in South-East Asia, the other B75 serotype alleles, *HLA-B\*15:08*, *HLA-B\*15:11*, and *HLA-B\*15:21*, have also been reported in association with CBZ-induced SJS/TEN (6). In some studies, an association between *HLA-B\*15:02* and SJS/TEN caused by phenytoin and phenobarbital has also been shown, but the overall evidence is weak. Nevertheless, these anticonvulsants should be avoided in patients who carry the allele as other alternatives are available. Similarly, oxcarbazepine and eslicarbazepine should be avoided in patients positive for *HLA-B\*15:02*.

The population frequency of *HLA-B\*15:02* is rare outside of some South-East Asian countries, and therefore it has not been identified as a predisposing factor in other ethnic groups. Instead, *HLA-A\*31:01* has been shown to predispose to CBZ hypersensitivity in Northern European and Japanese patients, and in several other ethnic groups, reflecting the higher global population frequency of the *HLA-A\*31:01* allele (6). The predisposition with *HLA-A\*31:01* is seen with several clinical phenotypes associated with CBZ use including maculopapular exanthem, DRESS, SJS/TEN and liver injury, in contrast to the association with *HLA-B\*15:02* which is with SJS/TEN only. Indeed, even in Chinese patients, *HLA-A\*31:01* predisposes to maculopapular reactions and DRESS (6). The reasons for the different phenotypic manifestations seen with *HLA-B\*15:02* and *HLA-A\*31:01* are unclear (see table 1). The association with *HLA-A\*31:01* seems to be strongest with CBZ-induced DRESS (7), and interestingly, it has recently been shown that *HLA-B\*57:01* may be a predisposing factor for CBZ-induced SJS/TEN in Northern Europeans (7). A prospective cohort study in Japan has shown that pre-prescription genotyping for *HLA-A\*31:01* and avoiding the use of CBZ in positive patients reduces the incidence of hypersensitivity reactions, although the effect was not as marked as with *HLA-B\*15:02* (6). *HLA-A\*31:01* is included in the drug label for CBZ by many drug regulatory agencies for information, unlike *HLA-B\*15:02*, which is recommended for typing prior to CBZ use. By contrast, guidelines are now recommending acting on both HLA alleles when prescribing CBZ (6).

There are many studies showing associations with other HLA alleles for the other older anticonvulsants, but these have usually been weak and/or not replicated. This is certainly true of lamotrigine hypersensitivity where no genetic screening tests currently exist. Indeed, the only preventive approach for lamotrigine hypersensitivity is to start at a low dose and escalate the dose slowly. A recent study in Chinese patients suggested that *HLA-A\*24:02* may be a common risk factor for cutaneous ADRs, but the associations were weak (P values ranging from 0.023 to 0.005), and did not reach the threshold for genome-wide significance, in contrast to *HLA-B\*15:02*, where the P value was 10-15 in the same study (8). No studies have been undertaken with the newer anticonvulsants such as zonisamide and rufinamide.

**Genetic predisposition outside HLA**

A genome-wide association study (GWAS) in Taiwanese patients with phenytoin-induced serious cutaneous adverse reactions identified *CYP2C9\*3* as a predisposing allele. This was replicated in Japanese and Malaysian patients (9). Functionally, this is biologically plausible since phenytoin is metabolised by CYP2C9, and decreased clearance of phenytoin was detected in *CYP2C9\*3* carriers. In Northern Europeans, a GWAS identified an association between phenytoin-induced maculopapular exanthem and the complement factor H-related 4 gene (10) - functional evaluation is needed to fully understand the biological plausibility of this association. A more recent GWAS in Northern Europeans with serious CBZ-induced reactions showed an association with the anaplastic lymphoma kinase (ALK) gene (7), although again, validation in other cohorts and functionally is required.

There has also been interest in the role of T cell receptor variation in predisposing to CBZ hypersensitivity, which is important since an immune reaction to CBZ requires an immunological synapse being formed between the HLA allele and the T cell receptor. In Taiwanese patients with CBZ-induced SJS/TEN, VB-11-ISGSY was the most common T cell receptor clonotype identified (6). However, this finding has not been replicated, and studies with other drug-induced hypersensitivity reactions has shown more polyclonal T-cell receptor usage. Additionally, it is also not known whether the T cell receptor repertoire changes as the reaction progresses and whether T-cell receptor usage is the same in the target tissue, for example in skin in patients with TEN, as in circulating T cells, which have been the source of most of the mechanistic work undertaken to date.

**Conclusions and further research**

Although the findings of the genetic predisposition to CBZ and phenytoin hypersensitivity reactions have been striking, much more work needs to be undertaken to further understand anticonvulsant hypersensitivity. Table 1 highlights some of the areas for further research. Key amongst these is an understanding of the mechanisms of how drugs and their antigens are presented by immune cells to lead to the immune reaction. There is evidence for antigen presentation of both the parent drug and its reactive metabolites, but whether both are important *in vivo*, how this differs between different phenotypes, and between different HLA alleles is unknown. It is also likely that genetic factors outside the HLA region are important, but unlike the HLA findings, the effect size is likely to be lower. This will therefore require studies with larger patient numbers – given the rarity of phenotypes seen with anticonvulsant hypersensitivity, this will only be possible through multi-centre international collaboration. It is also important to note that while genetic predisposing loci prevent serious CBZ-related reactions, a significant proportion of patients would never have developed the reaction even though they carried the risk allele(s). However, this may be acceptable if there are suitable equally efficacious alternative anticonvulsants available. Furthermore, in the case of *HLA-A\*31:01*, carriage of the risk allele does not completely preclude the use of carbamazepine where it is needed (6) but allows for identification of at-risk patients who can be more closely monitored. Finally, most of the work so far has focused on the older anticonvulsants, and as there is increased usage of the newer drugs, it is important that multi-centre prospective collections of biological samples from cases and controls treated with the newer agents is considered.

**References**

(1) Borrelli, E.P., Lee, E.Y., Descoteaux, A.M., Kogut, S.J. & Caffrey, A.R. Stevens-Johnson syndrome and toxic epidermal necrolysis with antiepileptic drugs: An analysis of the US Food and Drug Administration Adverse Event Reporting System. *Epilepsia* **59**, 2318-24 (2018).

(2) Frey, N. *et al.* The risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs. *Epilepsia* **58**, 2178-85 (2017).

(3) Chung, W.H. *et al.* Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* **428**, 486 (2004).

(4) Lin, C.W., Huang, W.I., Chao, P.H., Chen, W.W. & Hsiao, F.Y. Temporal trends and patterns in carbamazepine use, related severe cutaneous adverse reactions, and HLA-B\*15:02 screening: A nationwide study. *Epilepsia* **59**, 2325-39 (2018).

(5) Chen, Z., Liew, D. & Kwan, P. Effects of a HLA-B\*15:02 screening policy on antiepileptic drug use and severe skin reactions. *Neurology* **83**, 2077-84 (2014).

(6) Phillips, E.J. *et al.* Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. *Clin Pharmacol Ther* **103**, 574-81 (2018).

(7) Nicoletti, P. *et al.* Shared Genetic Risk Factors Across Carbamazepine-Induced Hypersensitivity Reactions. *Clin Pharmacol Ther*, (2019).

(8) Shi, Y.W. *et al.* HLA-A\*24:02 as a common risk factor for antiepileptic drug-induced cutaneous adverse reactions. *Neurology* **88**, 2183-91 (2017).

(9) Chung, W.H. *et al.* Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA* **312**, 525-34 (2014).

(10) McCormack, M. *et al.* Genetic variation in CFH predicts phenytoin-induced maculopapular exanthema in European-descent patients. *Neurology* **90**, e332-e41 (2018).

**Table 1**

**Some further research avenues in understanding anticonvulsant hypersensitivity**

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| --- | --- |
| Research avenues | Comments |
| Genetic associations* Identify HLA alleles with other anticonvulsants
* Identify non-HLA genetic factors with all anticonvulsants
* Identify genetic predisposing factors for the new anticonvulsants
* Clearly identify key characteristics of any genetic test including sensitivity, specificity, positive and negative predictive values
 | Need for larger patient numbers to identify HLA associations with other anticonvulsants such as lamotrigine, and non-HLA genetic factors. New anticonvulsant cases need to be identified and studied for both HLA and non-HLA genetic factors. Also important here is the identification of factors that protect those patients with risk HLA alleles from the hypersensitivity reactions. This is only likely to be possible through multi-centre international collaboration. |
| Mechanisms of hypersensitivity reactions* Mechanism of antigen presentation
* Role of T cell receptor clonotype
* Mechanism of the relationship between HLA alleles and organ-specificity
* Mechanisms of severity of reaction
 | Will require a variety of more modern techniques including Xray crystallography, immunopeptidomics, mass cytometry, T cell receptor sequencing and single cell sequencing to understand the nature of the immune response. It is also important to understand the phenotypes of the immune cells at the site of reaction in comparison to those found in circulating blood (which has been the focus of most of the studies to date). |
| Barriers to implementation* Evidence requirements for implementation
* Cost effectiveness
* Educational requirements
* Pre-emptive approaches
 | Even with very striking findings, implementation is not straightforward. There is a need for implementation science to understand why this is the case, and what can be done overcome the barriers. This should include research into the possibility of moving from our current reactive approach to pre-emptive approaches with the availability of genotypes being embedded within electronic healthcare records. |
| Policy research* Requirements for drug label changes
* Requirements and acceptability of guidelines
* Re-imbursement policies
 | More work in the area of policy research would help identify pathways that facilitate uptake of new preventive strategies into clinical practice, and will require collaborative work with regulators, guidelines producers, and healthcare managers and payers. |

**Figure legend**

**Figure 1**

Categorisation of hypersensitivity reactions associated with anticonvulsants according to knowledge of the clinical manifestations so far identified, and the HLA and non-HLA factors that have been discovered.

**Supplementary Material**

**Supplementary reading list.**

Additional references which are relevant to this article.