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Association of HLA-B*1502 allele and carbamazepine-induced severe adverse cutaneous drug reaction among Asians, a review

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Abstract

Strong association between HLA B*1502 and carbamazepine-induced Steven-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) was demonstrated among Han Chinese in 2004. Studies from Europe showed that the HLA B*1502 is not a universal marker for SJS/TEN, but is ethnicity specific for Asians. Reports across Asia has shown that the prevalence of HLA B*1502 is high among Han Chinese (5-15%), Malays (12-15%), and Thais (8-27%), but low among Japan, Korea, Sri Lanka, and most ethnic groups in India. Other than Han Chinese, the association between HLA B*1502 and carbamazepine-induced SJS-TEN is also seen among the Thais and Malay. There is urgent need for further studies to determine the prevalence of SJS/TEN, and HLA B*1502 in the various ethnic groups in Asia, and its association with carbamazepine-induced SJS-TEN in each of these ethnic groups. In view of the significant morbidity and mortality in SJS-TEN, facilities should be developed to allow for screening of HLA B*1502 before carbamazepine is prescribed to the Hans Chinese, Malays and Thais. For those who experience no adverse cutaneous reaction after 3 months use of carbamazepine, the risk of SJS/TEN is low, and the drugs can be continued.

INTRODUCTION

In 2004, Chung *et al*[1] from Taiwan reported from their Han Chinese patients, a strong association between carbamazepine (CBZ)-induced Stevens-Johnson syndrome (SJS) and HLA-B*1502. The HLA-B*1502 allele was seen in all 44 patients with CBZ-SJS, only 3% of CBZ-tolerant patients, and 8.6% of the normal population. The same group later expanded the study, and showed that the strong association of CBZ is with severe cutaneous drug reaction, i.e. SJS and toxic epidermal necrolysis (TEN), but not with the milder maculopapular eruption and hypersensitivity syndrome.[2] Lonjou *et al* reported from their 12 European patients with CBZ-induced SJS/TEN, that only 4 had a HLA-B*1502, and all the 4 had an Asian ancestry.[3] The study thus indicates that HLA-B*1502 is not a universal marker for CBZ-induced SJS/TEN, but is ethnicity specific. The US Food and Drug Administration (FDA) has published an alert to healthcare professionals on the use of CBZ to Asians.[4] As CBZ-induced adverse skin reaction is a relatively common clinical problem among some Asians with potential fatal outcome, this paper aims to review the results of study to date, the important clinical issues to be clarified, and guidelines to physicians in their clinical practice in Asia.

SEVERE ADVERSE CUTANEOUS DRUG REACTION

Severe adverse cutaneous drug reaction (ACDR), for example SJS and TEN are life-threatening skin reactions to medications. TEN is an acute dermatologic disease, characterized by widespread erythematous macules and targetoid lesions; full-thickness epidermal necrosis, at least focally; and involvement of more than 30% of the cutaneous surface. SJS may have full-thickness epidermal necrosis, but with lesser detachment of the cutaneous surface; and mucous membrane involvement.[5-6]

Maculopapular exanthema and hypersensitive skin syndrome are other spectrum of cutaneous drug reactions. Maculopapular exanthema is characterized by cutaneous fine pink macules and papules, lesions which usually fade within 1–2 weeks following cessation of drug treatment. Hypersensitive skin syndrome is characterized by multi-organ involvement (e.g. hepatitis and nephritis) accompanied by systemic

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manifestations (e.g. fever, arthralgia, eosinophilia and lymphadenopathy) in addition to skin rashes. According to the clinical morphology, SJS/TEN belong to the group of bullous cutaneous adverse drug reactions, whereas Maculopapular exanthema and hypersensitive skin syndrome are non-bullous reactions.[2]

Among drugs used long term, the greatest risk of SJS/TEN are seen in the first 2 months of use. The agents are mostly antiepileptic drugs e.g. CBZ, phenobarbital, phenytoin, valproic acid and others; e.g. oxicam nonsteroidal anti-inflammatory drugs, allopurinol, and corticosteroids.[7]

SJS may prove fatal in about 5% of patients; and TEN in as many as 40% of patients. Sepsis and respiratory distress are the most common complications and ultimately the direct causes of death.[8-9]

Survivors of SJS/TEN may experience numerous long-term sequelae; the most disabling are those involving the eye. As many as 40% of TEN survivors have residual potentially disabling lesions, that may cause blindness. Cutaneous lesions may resolve with a patchwork of hyperpigmentation and hypopigmentation. Lesions in genitourinary system may lead to phimosis or vaginal synechiae.

CARBAMAZEPINE-INDUCED ADVERSE CUTANEOUS DRUG REACTION

ACDR is very common, comprise 10 to 30% of all reported adverse drug reaction[10-12] and 2-3% of all hospitalization.[13-15] Incidence of SJS/TEN is slightly higher in two Asian studies from Singapore and Malaysia, 8 per million person year[16-17], as compared to 0.4-7.4 per million person year in Caucasian population.[3,7,18-22] However, CBZ constitutes 25-33% of all SJS/TEN in the Singapore and Malaysian studies mentioned above[16-17], much higher compared to 5-6% in Caucasian population.[7,21,23] According to FDA, post-marketing adverse events reported to the WHO and CBZ manufacturers pointed to a much higher rates of SJS/TEN, about 10 times higher in some Asian countries, e.g. Malaysia, Thailand, Taiwan and Philippines.[4,24] Based on cumulative estimated reported rates between 2000 and 2006 by Novartis, CBZ manufacturer, the incidence of SJS/TEN were 4.1-5.9 per 10,000 patient year exposure in some Asian countries, as compared to 0.2-0.9 in European countries and USA.[24] Among new users of CBZ, ACDR was estimated to occur in 1 to 6 per 10,000 in the Caucasian population[20,25-27], as compared to 25 per 10,000 in Taiwan.[28]

The greatest risk of CBZ-induced severe ACDRs are noted within the first two months.[7] The risk of SJS/TEN is higher with increasing dose of lamotrigine[29], but the relation between risk of SJS/TEN and dose is unknown in CBZ.

ASSOCIATION BETWEEN HLA B*1502 AND CARBAMAZEPINE-INDUCED ADVERSE CUTANEOUS DRUG REACTION

The prevalence of HLA B*1502 is high in some Asian populations as shown in Table 1. It ranges from 12.0-15.7% in Malay populations from Malaysia and Singapore; 5.7-14.5% in Han Chinese in Taiwan, Hong Kong, Malaysia, Singapore; 8.5-27.5% in Thai, and >10% in Vietnamese. However, the prevalence is low in Sri Lanka, Japan and Korea; similar to prevalence in Europe, American Caucasian and Native and South America. Based on the allele frequency in the U.S. National Marrow Donor Program, similar pattern of HLA-B*1502 frequency was noted; in which the frequency varies widely among the various ethnic Asians in U.S., and essentially absent among US Caucasians, Hispanics, Native Americans and Africans.[24]

The association between CBZ-induced SJS and HLA B*1502 was extremely high among the Han Chinese in the original[1] and follow-up[2] Taiwan studies, with odd ratio of 2,504 (95% CI 126 to 49,522) and 1,357 (95% CI 193–8,838) respectively. Similar result was also seen among the Han Chinese in Hong Kong.[36] Studies in Malay and Thai populations showed a similar strong association between CBZ-induced SJS and HLA B*1502, the odd ratio being 16.15 for the Malays in Malaysia.[38-41] However, there was no significant association between HLA B*1502 and those with CBZ-induced maculopapular eruption and hypersensitivity syndrome[2,36], which is probably due to different mechanism from SJS/TEN.

Similar association of HLA B*1502 and CBZ hypersensitivity was not demonstrated in Caucasian population.[3,34]

According to FDA, the risk of SJS/TEN in HLA-B*1502 positive patients exposed to CBZ in Taiwan is 5%, based on postmarketing data on cases per patient-year exposure.[4] Based on an estimation by Hung *et al*, in which about 50 new cases of CBZ-SJS/TEN per year occur in Taiwan, out of 20,000 new CBZ users, the risk of CBZ-induced SJS/TEN in Taiwan is one in 400 patients.[28]

Table 1: Incidence of adverse cutaneous drug reactions and prevalence of HLA B*1502 in normal population and carbamazepine-induced Steven-Johnson syndrome and toxic epidermal necrolysis

Country/Region	Incidence of severe ACDR, per million persons year	Incidence of HLA B*1502 in normal population, percent	Incidence of HLA B*1502 in CBZ-SJS/TEN, percent
USA	In general 2.6-7.1[19], Boston 4.2[18] (2 per 100,000 patient year exposure)[24]	0% in Caucasian and native American[30-32], Asian 4.9[33]	
Europe	In general, 2-3[3]; Sweden 0.4, French 1.2 Germany 2.03 (2-9 per 100,000 patient year exposure)[24]	Rare (1-2)[7,28,34] Ireland 0[10]	
South America		Argentina 0[35]	
South Africa	(3 per 100,000 patient year exposure)[24]		
Asia			
• Taiwan[1-2]	Han Chinese 8 (59 per 100,000 patient year exposurre)[24]	Han Chinese 8.6, Thai 5.7-8.6	Han Chinese 100
• Hong Kong[36]		14.5	Han Chinese 100 (4 patients)
• Singapore[37]		Chinese 5.7, Malay 12.0, Indian 8.3	
• Malaysia[38]	(41 per 100,000 patient year exposure)[24]	Malay 15.7, Chinese 5.7, Indian 0, Myanmese 100 (1 patient)	Malay 75, Indian 100
• Thailand		8.5-27.5[10,39-40]	83.3[41]
• Vietnam		>10[42]	
• Indonesia		16	
• Philippines	(55 per 100,000 patient year exposure)	Ivatan (minority) 36[#]	
• India		Mumbai 1.9[43], Kandesh 6[44], Tamil Nadu 0[45], Bhil 4[46], Parsi 0[47] Punjab 1[48]	
• Sri Lanka		Rare[49]	
• Japan	(17 per 100,000 patient year exposure)[24]	0.2[#]	
• Korea		0.4[#]	

CBZ: carbamazepine, SJS: Steven-Johnson syndrome, TEN: toxic epidermal necrolysis
Data in bracket was quoted from Novartis CBZ SJS/TEN Reports 2000-2006, per 100,000 patient exposure year.[24]
Allele frequency based on volunteers in the U.S. National Marrow Donor Program.[24]

Figure 1: Area with high prevalence of HLA B*1502 (>5%), indicated as grey.

POSSIBLE MECHANISM FOR CARBAMAZEPINE-INDUCED ADVERSE CURANEOUS DRUG REACTION

The mechanism by which CBZ causes ACDR is not well understood. Potential defects in the enzymes responsible for bioactivation and detoxification of CBZ have been proposed.[50] CBZ is bioactivated by hepatic cytochrome P450 enzymes, which generate various potentially reactive metabolites, such as CBZ 10,11-epoxide, 3-hydroxy CBZ, 2-hydroxy CBZ, and CBZ 2,3-epoxide [51-52]. Most of the reactive epoxides are detoxified to non-toxic dihydrodiols by liver microsomal epoxide hydrolase 1 (EPHX1) or to glutathione conjugates by glutathione transferase.[53-54]

ACDR triggered by CBZ is postulated to immune related because infiltrating inflammatory cells can be detected in the skin lesions.[55-56] CD8+ T-cell-mediated cytotoxic responses appear to be the major event in SJS/TEN.[57] There is evidence supporting the view that ACDR involve major histocompatibility complex (MHC)-dependent presentation of its metabolites for T cell activation.[57-58] The HLA-B allel can elicit immune responses by presenting endogenous antigens to the cytotoxic T cells [59-60], resulting in proliferation of the cytotoxic cells.[61]

Cross-reactivity among the aromatic antiepileptic drugs (CBZ, phenytoin, phenobarbital) in inducing ACDR is recognized, but has not been observed between aromatic antiepileptic drugs and lamotrigine.[62] However, in addition to CBZ, HLA-B*1502 allele was found in patients with lamotrigine and phenytoin-induced SJS/TEN as well, though the number were small.[36,63] Whether this implies a similar immune response against the different antiepileptic drugs will need to be confirmed in larger studies.

HLA-B has been demonstrated to be significantly related to various drug related SJS/TEN, e.g. HLA-B*5701 in abacavir hypersensitivity[64], HLA B*5801 in allopurinol and B1513 in phenytoin. This implies the important role of HLA-B in the pathogenesis of ACDR.

RECOMMENDATIONS FOR RESEARCH IN ASIA

Asia is a large region with 60% of world population. The region is the home of many national groups with different culture and ethnicity. Data from the WHO Uppsala Monitoring Center (WHO-UMC) and Novartis CBZ-SJS/TEN reports 2000-2006 showed that the incidence of ACDR induced by CBZ was high among some Asian countries.[24]

However, the incidence is not known in many geographical regions and ethnic groups, therefore it is important to document the incidence of ACDR induced by CBZ in these areas. As the importance of HLA B*1502 as marker of CBZ-induced SJS/TEN is being established particularly among Han Chinese, and the prevalence of HLA B*1502 in various ethnic groups are being determined, there are still large parts of Asia where the prevalence of HLA B*1502 is not known. This is for example, the Han and non-Han Chinese from different parts of China, Filipinos, various ethnic groups in Indonesia, Pakistan, Bangladesh, Myanmar, Cambodia and Lao PDR. The determination of the prevalence of HLA B*1502 in these ethnic groups is thus of high priority.

To-date, the significance of HLA B*1502 as a marker for CBZ-induced SJS/TEN is only established among the Han Chinese, less so among the Malays and Thais. As HLA B*1502 as a marker of CBZ-induced SJS/TEN is ethnicity specific, there is also a need to determine the relationship between HLA B*1502 and CBZ-induced SJS/TEN in other ethnic groups in Asia.

There are many unanswered questions in CBZ-induced ACDR and HLA B*1502 waiting to be explored. How CBZ dosage affects the likelihood and timing of ACDR is uncertain. The reason why ACDR is delayed in certain drugs such as CBZ as compared to early ACDR in antibiotic is also not known. The exact mechanism of how CBZ modulates cytotoxic activity via HLA gene is also poorly understood.

Other questions to be explored include the role of other HLA-B subtypes in CBZ-induced SJS/TEN, significance of HLA B*1502 and other HLA subtypes in ACDR induced by other antiepileptic drugs, e.g. phenytoin and lamotrigine.

RECOMMENDATION FOR USE OF CARBAMAZEPINE

As CBZ is an effective, safe and cost effective antiepileptic drug, the recent finding of HLA-B*1502 as marker of CBZ-induced SJS/TEN indicates that it is of high priority to develop facilities for testing of HLA-B*1502 in clinical practice involving Han Chinese, Malays and Thai patients. Patients of these ethnic groups should be screened for the HLA-B*1502 allele before starting treatment with CBZ. If tested positive, CBZ should be avoided. However, it should be noted that patients who are tested positive for HLA-B*1502 may be at increased risk of SJS/TEN from other antiepileptic drugs e.g. lamotrigine and phenytoin.[36,63] It is probably advisable to avoid other antiepileptic drugs also known to cause SJS/TEN, namely lamotrigine, phenytoin and phenobarbital.[25]

The median duration of developing CBZ-induced SJS/TEN is 25 to 90 days.[7] Patients who have been taking CBZ for more than 3 months without developing skin reactions are at low risk of CBZ-induced ACDR. Therefore, use of CBZ can be continued without screening.

In conclusion, HLA B*1502 has recently been linked to CBZ-induced SJS/TEN in some Asian groups. Screening of HLA B*1502 in these ethnic groups before use of CBZ is recommended. Determination of prevalence of HLA B*1502 and its association with CBZ-induced SJS/TEN in the different ethic groups is thus of high priority for epilepsy care in Asia.

REFERENCES

1. Chung WH, Hung SI, Hong HS, *et al*. A marker for Stevens–Johnson syndrome. *Nature* 2004;428.
2. Hung SI, Chung WH, Jee SH, *et al*. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenetics and Genomics* 2006; 16:297–306.
3. Lonjou C, Thomas L, Borot, N, *et al*. A marker for Stevens-Johnson syndrome: ethnicity matters. *Pharmacogenomics J* 2006; 6(4):265-8.
4. FDA Alert. Information for Healthcare Professionals Carbamazepine (marketed as Carbatrol, Equetro, Tegretol, and generics). Available in URL: http://www.fda.gov:80/cder/drug/InfoSheets/HCP/carbamazepineHCP.htm
5. Bastuji-Garin S, Rzany B, Stern RS, *et al*. Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* 1993;129:92-6.
6. Roujeau JC. The spectrum of Stevens-Johnson syndrome and toxicepidermal necrolysis: a clinical classification. *J Invest Dermatol* 1994; 102(6):28S-30S
7. Roujeau JC, Kelly JP, Naldi L, *et al*. Medication use and the risk of Stevens–Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; 333:1600–7.
8. Roujeau JC, Guillaume JC, Fabre JP, *et al*. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Arch Dermatol* 1990 ;126:37-42.
9. Revuz JR, Penso D, Roujeau JC, *et al*. Toxic epidermal necrolysis: clinical findings and prognostic factors in 87 patients. *Arch Dermatol* 1987; 123:1160-4.
10. Faich GA, Knapp D, Dreis M, and Turner W. National adverse drug reaction surveillance. *J Am Med Assoc* 1987; 257:2068–70.
11. Naldi L, Conforti A, Venegoni M, *et al*. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999;

48:839–46.
12. Stewart RB, May FE, Cullen SI. Dermatologic adverse drug reactions in hospitalized patients. *Am J Hosp Pharm* 1979; 36:609–12.
13. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions. A report from the Boston Collaborative Drug Surveillance Program on 15,438 consecutive inpatients, 1975 to 1982. *JAMA* 1986; 256:3358–63.
14. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol* 2001; 137:765–70.
15. Rademaker M, Oakley A, Duffill MB. Cutaneous adverse drug reactions in a hospital setting. *NZ Med J* 1995; 108:165–6.
16. Khoo AKM, Foo CL. Toxic epidermal necrolysis in a burns centre: A 6-year review. *Burns* 1996; 22:275–8.
17. Kamaliah MD, Zainal D, Mokhtar N, Nazmi N. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis in northeastern Malaysia. *Int J Dermatol* 1998; 37:520–3.
18. Chan HL, Stern RS, Arndt KA, *et al*. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxicepidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol* 1990; 126(1):43-7.
19. Strom BL, Carson JL, Halpern AC, *et al*. A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. *Arch Dermatol* 1991; 127(6):831-8.
20. Messenheimer J. Incidence of Stevens-Johnson syndrome and toxic epidermal necrolysis among new users of antiepileptic drugs. *Neurology* 2004; 62(7)(Suppl5):A352
21. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case-control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999; 353:2190-4.
22. Wolkenstein P, Revuz J. Drug-induced severe skin reactions. Incidence, management and prevention. *Drug Saf* 1995; 13(1):56-68.
23. Schopf E, Stuhmer A, Rzany B, *et al.* Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. *Arch Dermatol* 1991; 127(6):839-42.
24. Ronald Farkas, Clinical Review, Adverse Events of Carbamazepine. Available in URL: http://www.fda.gov/cder/foi/nda/2007/016608s098,020712s029,021710_ClinRev.pdf
25. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. *Neurology* 2005; 64(7):1134-8.
26. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. *Neurology* 1997; 49(2):542-6.
27. Vittorio CC, Muglĩa JJ. Anticonvulsant hypersensitivity syndrome. *Arch Intern Med* 1995; 155:2285–90.
28. Hung SI, Chung WH, Chen YT. HLA-B genotyping to detect carbamazepine-induced Stevens–Johnson syndrome: implic˜ations for personalizing medicine. *Personalized Med* 2005; 2:225–37.
29. Guberman AH, Besag FM, Brodie MJ, *et al*. Lamotrigine associated rash: risk/benefit considerations in adults and children. *Epilepsia* 1999; 40:985–91.
30. Faich GA, Knapp D, Dreis M, Turner W. National adverse drug reaction surveillance. *J Am Med Assoc* 1987; 257:2068–70.
31. Cao K, Hollenbach JA, Shi XJ, Shi WX, Chopek M, Fernández-Vina MA. HLA-A, -B and -Cw allele frequencies in an Asian population from the USA. *Human Immunology* 2004; 65(9-10):1194-6.
32. Cao K, Hollenbach JA, Shi XJ, Shi WX, Chopek M, Fernández-Vina MA. HLA-A, -B and -Cw allele frequencies in a Native Amerindian population from the USA. *Human Immunology* 2004; 65(9-10):1208-11.
33. Cao K, Hollenbach JA, Shi XJ, Shi WX, Chopek M, Fernández-Vina MA. HLA-A, -B and -Cw allele frequencies in an Asian population from the USA. *Human Immunology* 2004; 65(9-10):1194-6.
34. Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 2006; 7(6): 813-8.
35. Marcos CY, Theiler GC, Capucchio M, Fainboim L. HLA-A, -B, -DPB1, -DQA1, -DQB1 and -DRB1 allele frequencies in a Wichis Amerindian population from Argentina. *Human Immunology* 2004; 65(9-10):860-1.
36. Man CBL, Kwan P, Baum L, *et al*. Association between HLA-B*1502 Allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007; 48(5):1015–8.
37. Tang TF, Hou L, Chen M, *et al*. HLA Haplotypes in Singapore: A Study of mothers and their cord blood units. *Human Immunology* 2007; 68,430–8.
38. Chang CC, Too CL, Murad S, Hussein S. Association of HLA-B*1502 with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in Malaysian population. Proceeding in 7th Asian-Oceanian Epilepsy Congress, Xiamen. 2008
39. Romphruk A, Phongaen K, Chotechai J, Puapairoj C, Leelayuwat C, Romphruk AV. HLA-B*15 subtypes in the population of north-eastern Thailand. *European Journal of Immunogenetics* 2003; 30(2):153-8(6).
40. Han M, Tan Y, Guo Y, Romphruk A, Leelayuwat C, Stastny P. Allele Level typing of HLA-B locus by multiplexed single nucleotide extension (MSNE) and a study of B15 in different ethnic groups. *Human Immunology* 2004; 65(9-10)Suppl 1:S25
41. Loplumlert, J; Locharernkul, C; Shotelersuk, V; Limotai, C. A genetic screening of Steven Johnson syndrome from carbamazepine and phenytoin among people with epilepsy in Thailand**.** *Epilepsia 2007; 48(Suppl7):S127*
42. Hoa BK, Hang NT, Kashiwase K, *et al*. HLA-A, -B, -C, -DRB1 and -DQB1 alleles and haplotypes in the Kinh population in Vietnam. *Tissue Antigens* 2008; 71(2):127-34.

43. Shankarkumar U. HLA-A, -B and -Cw allele frequencies in a Maratha population from Mumbai, India India Mumbai Marathas. *Human Immunology* 2004; 65(9-10):954-6.
44. Shankarkumar U. HLA-A, -B and -Cw allele frequencies in a Pawra population from Khandesh, India. *Human Immunology* 2004; 65(9-10):952-3.
45. Shankarkumar U. HLA-A, -B and -Cw allele frequencies in a Nadar population from Tamil Nadu, India. *Human Immunology* 2004; 65(9-10):958
46. Shankarkumar U. HLA-A, -B and -Cw allele frequencies in a Bhil population from Western India. *Human Immunology* 2004; 65(9-10):960-1.
47. Shankarkumar U. HLA-A, -B and -Cw allele frequencies in a Parsi population from Western India. *Human Immunology* 2004; 65(9-10):992-3.
48. Rajalingam R, Parham P, Mehra NK, *et al*. HLA-A, -B, -Cw, -DQA1, -DQB1 and -DRB1 Alleles and KIR Alleles in a Hindu Population from Punjab, India. *Human Immunology* 2004; 65(9-10):958-60.
49. Johnson J, Thompson J, Hammond L, *et al*. HLA-A, B, DR and DQ Gene and haplotype frequencies in Sri Lankan Indian Tamils. Available in URL: http://www.wtail.org.uk/pdfdocs/P142/hfe%20poster.pdf
50. Leeder JS. Mechanisms of idiosyncratic hypersensitivity reactions antiepileptic drugs. *Epilepsia* 1998; 39 (Suppl 7):S8–S16.
51. Kerr BM, Thummel KE,Wurden CJ, Klein SM, Kroetz DL, Gonzalez FJ. Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol* 1994; 47:1969–79.
52. Madden S, Maggs JL, Park BK. Bioactivation of carbamazepine in the rat in vivo. Evidence for the formation of reactive arene oxide(s). *Drug Metab Dispos* 1996; 24:469–79.
53. Bellucci G, Berti G, Chiappe C, Lippi A, Marioni F. The metabolism of carbamazepine in humans: steric course of the enzymatic hydrolysis of the 10,11-epoxide. *J Med Chem* 1987; 30:768–73.
54. Lillibridge JH, Amore BM, Slattery JT, *et al*. Protein-reactive metabolites of carbamazepine in mouse liver microsomes. *Drug Metab Dispos* 1996; 24:509–14.
55. Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. *J Immunol* 1995; 155:462–72.
56. Nassif A, Bensussan A, Dorothee G, *et al*. Drug specific cytotoxic T-cells in the skin lesions of a patient with toxic epidermal necrolysis. *J Invest Dermatol* 2002; 118:728–33.
57. Nassif A, Bensussan A, Boumsell L, *et al*. Toxic epidermal necrolysis: effector cells are drug-specific cytotoxic T cells. *J Allergy Clin Immunol* 2004; 114:1209–15.
58. Schnyder B, Mauri-Hellweg D, Zanni M, Bettens F, Pichler WJ. Direct, MHC dependent presentation of the drug sulfamethoxazole to human alphabeta T cell clones. *J Clin Invest* 1997; 100:136–41.
59. Horton R, Wilming L, Rand V, *et al*. Gene map of the extended human MHC. *Nat Rev Genet* 2004; 5:889–99.
60. Pichler WJ. Modes of presentation of chemical neoantigens to the immune system. *Toxicology* 2002; 181–182:49–54.
61. Wu Y, Sanderson JP, Farrell J, *et al*. Activation of T cells by carbamazepine and carbamazepine metabolites. Journal of Allergy and Clinical Immunology 2006; 118:233–41.
62. Arroyo S, de la Morena A. Life-threatening adverse events of antiepileptic drugs. *Epilepsy Research* 2001; 47:155–74.
63. Chang CC. Human leukocyte antigens in toxic epidermal necrolysis and Steven Johnson syndrome in Malaysian population. Advanced Master of Dermatology Thesis, Universiti Kebangsaan Malaysia
64. Mallal S, Nolan D, Witt C, *et al*. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; 359:727–32.