

DR MOHAMMED FAIZAL BAKHTIAR (Orcid ID : 0000-0002-0203-9510)

Article type : Research Letter

Title: Incidental Pharmacogenetics Findings in an HLA-related Research: Considerations for Primary Prevention

Running Title: Incidental Findings for Primary Prevention

Authors: Faizal Bakhtiar^{1,2*}, Chun-Lai Too³, Min-Moon Tang⁴, Salsabil Sulaiman³, Lay-Kim Tan³, Nurul Aain Ahmad-Fauzi³, Fan-Yin Kwok⁵, Shahnaz Murad⁶, Giriappanavar Chandrashekar Rayyapa²

¹ Allergy Unit, Allergy & Immunology Research Center, Institute for Medical Research, Ministry of Health Malaysia. Kuala Lumpur, Malaysia.

² Faculty of Medicine, Universiti Kuala Lumpur Royal College of Medicine Perak, Ipoh, Perak, Malaysia.

³ Immunogenetic Unit, Allergy & Immunology Research Center, Institute for Medical Research, Ministry of Health Malaysia. Kuala Lumpur, Malaysia.

⁴ Department of Dermatology, Kuala Lumpur Hospital, Ministry of Health Malaysia. Kuala Lumpur, Malaysia.

This article has been accepted for publication and 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/cea.13347

This article is protected by copyright. All rights reserved.

⁵Anesthetic Allergy Clinic, Department of Anesthesia and Intensive Care, Kuala Lumpur Hospital, Ministry of Health Malaysia. Kuala Lumpur, Malaysia.

⁶Ministry of Health Malaysia. Level 12, Block E7, Parcel E, Federal Government Administrative Center. 62950 Putrajaya. Malaysia.

***Correspondence:**

Faizal Bakhtiar MD, Allergy Unit, Allergy & Immunology Research Center, Institute for Medical Research, Ministry of Health Malaysia. Kuala Lumpur, Malaysia

Email: drfuzzy73@gmail.com/faizal@imr.gov.my

Authorship: FB and TCL conceived and designed the study. FB, TCL, SS, TLK and NAAF performed the laboratory experimental work and analyzed the genetic data. FB, TMM and KFY recruited the participants, performed the clinical experimental work and collected the samples. FB, TCL, SM and GCR reviewed the literature. SM and GCR provided expert consultations on the subject matter. FB drafted the manuscript. All authors critically appraised the manuscript and contributed to the final approval of the manuscript.

Acknowledgements: We would like to thank the Director General of Health Malaysia for his permission to publish this article. We also thank all the subjects who volunteered to participate in this project and, all the clinical and laboratory staff that were involved in this pilot project.

This study was financially supported by Ministry of Health Malaysia: NMRR-16-884-31002/JPP-IMR 16-028

Conflict of Interest Statement: All the authors declare no conflict of interest

To the Editor,

Hypersensitivity drug reactions (HDRs) are an immense public health problem where significant proportions may lead to mortality. HDRs can manifest in various phenotypes, mainly cutaneous reactions that range from the mild; i.e. exanthem, urticaria, and angioedema to the critical; i.e. severe cutaneous adverse reactions (SCARs). SCARs are life-threatening reactions that include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS) and less commonly, acute generalized exanthematous pustulosis (AGEP). Previously, these reactions were unavoidable as they are linked to the intrinsic properties of drugs and an individual's genetic predisposition. Nevertheless, with the advent of pharmacogenomics and the vast pharmacogenetic studies performed in the last two decades, this is set to change in future.

Today, pharmacogenomics is viewed as a highly substantial field for improving drug therapy and prescription of personalized medicine. Furthermore, technological advancement in pharmacogenomics research has greatly improved our understanding of adverse drug reactions. Pharmacogenomics research not only tailors therapeutics to an individual's make-up (disease phenotype, genetic, environmental and clinical manifestations), but also maximizes success of drug therapy and minimizes any potential adverse effects [1].

The United States Food and Drug Administration has included information about 43 pharmacogenomics biomarkers in the labels of 155 drugs [2]. Some early adoption of pharmacogenomics screening include Her2/neu testing for metastatic breast cancer patients to determine responsiveness to Herceptin[®] and the use of thiopurine 6-mecaptopurine testing to manage the treatment of children with acute lymphoblastic leukaemia [2]. Several genetic studies have demonstrated that certain human leukocyte antigen (HLA)-B alleles are predisposed to HDRs that are deemed actionable including HLA-B*15:02 (carbamazepine), B*15:13 (phenytoin), B*58:01 (allopurinol) and B*57:01 (abacavir) mainly in non-Caucasian populations [3, 4] (Supplementary Table S1). Screening for these specific HLA-B alleles has been recommended before treatment initiation. However, there are no clear guidelines on the alert mechanism when the HDR-related HLA alleles were found incidentally, during an HLA-related genetic research. In this study, we aimed to formulate a suitable alert system to assist primary prevention of potential HDRs when incidental findings of HLA-B associated alleles for carbamazepine, phenytoin, allopurinol and/or abacavir were observed in an HLA-related genetic research.

A total of 68 subjects were recruited in a case-control study investigating the HLA associations with non-steroidal anti-inflammatory drug induced urticaria/angioedema in the Malay ethnic group between 2016 and 2017. Subjects were recruited from Allergy, Anesthetic and Dermatology clinics at a tertiary public hospital. The demographic and clinical characteristics of the studied subjects is presented in Supplementary Table S2. All subjects were genotyped for the four-digit HLA-B alleles (LAB Type XR Class I B locus Typing Test, One Lambda Inc., CA, USA). The observed incidental positive findings of HLA-B*15:02, B*15:13, HLA-B*58:01 and HLA-B*57:01 alleles were recorded. Subjects were informed of the incidental findings and their potential associated clinical implications were explained. The Medic Alert Foundation Malaysia (Supplementary Figure S1)

notification and registration form was issued to the respective individuals, with details of positive HLA-B alleles found and risk of reaction to respective drug for application of their Medic Alert bracelet. The subjects were followed up to see if the bracelet has influenced the clinicians' decision in pharmacotherapy. Informed written consent was obtained from all participants. This study was approved by the Medical Research Ethics Committee, Ministry of Health Malaysia [(10) KKM/NIHSEC/P-16-838/24062016].

In this study, we found that the HLA-B alleles did not deviate from the Hardy-Weinberg equilibrium for all studied subjects ($p > 0.05$). Overall, 33 of the 68 studied subjects (48.5%) were positive to at least one of the implicated HLA-B alleles (HDRs group, $n=19/35$, 54.3%; drug-tolerant group, $n=14/33$, 42.4%, respectively). The HLA-B*15 family comprising HLA-B*15:02, 15:08, B*15:11, B*15:18 and B*15:21, which were collectively associated with carbamazepine-induced SJS and TEN, was the commonest implicated HLA-B allele found in this study ($n=25/68$, 36.8%). Of these 25 HLA-B*15 positive individuals, 20 individuals (80%) were carriers of HLA-B*15:02 allele (Figure 1). Medic Alert forms were issued to all identified genetically-at-risk individuals and 93.9% of these individuals agreed to obtain the Medic Alert bracelet to prevent possible future reactions upon treatment with the specified drug(s) if needed. To date, the use of the medic alert bracelet has influenced the decision of clinicians in 4.4% ($n=3$) for allopurinol and/or carbamazepine therapy.

The frequency of incidentally observed implicated HLA-B alleles in this selected population was higher (48.5%) than previously reported in population-based studies. However, formal guidelines on disclosure of incidental findings to research subjects are limited, impeding responsible reporting from researchers. The American College of Medical Genetics and Genomics (ACMG) recommended that the management of incidental findings

be bound to the ethical principles of respect for persons, beneficence, justice and fairness, as well as intellectual freedom and responsibility [5].

In the context of the current study, the question of disclosure of the incidental findings while maintaining the participants' autonomy is considered minimal, as participation in the drug hypersensitivity genetic study was voluntary. The subjects were not tested out of necessity as in the case for diagnostic procedures. Nevertheless, researchers are encouraged to counsel participants during the initial stages of informed consent about future testing on family members, as genetic testing is relatively expensive. As endorsed by the ACMG guideline [5], the implicated HDRs-associated HLA-B alleles observed in this study had met the accepted criteria of scientific and clinical validity.

The HDR-associated HLA-B* allelic frequencies distribution in Malay population, HDR phenotype(s), negative predictive value (NPV) and positive predictive value (PPV) of the related drug and approximate number needed to test (NNT) to prevent one case of related HDR are presented in Supplementary Table S3. The PPV ranges from 2.7% and 76.7% and NPV is observed to be more than 97% for the related drug in the studied population. Taken together, the low to moderate PPV and high NPV with severity of HDR shows that benefits of HLA screening outweigh the risks, supporting the recommendation by the Clinical Pharmacogenetics Implementation Consortium (CPIC). Thus, disclosure of incidental HLA findings in our study serves as a clinical utility to the study participants [5]. It is noteworthy that potential benefits and risks are associated with HLA screening to patients. A benefit of genetic testing is the avoidance of adverse effects in carriers of HDR-associated HLA-B* alleles, reducing the incidence of life-threatening reactions. In addition, these at-risk individuals may be prescribed alternative drugs that are relatively effective and safer. However, the risk of genotyping error during HLA-screening could have significant

healthcare impacts. These include misleading risk variants identification and unnecessary contraindication of the respective drug in patients who do not develop HDR.

As the current practice of the allergy card in Malaysia is strictly for secondary prevention, we opted for the medic alert bracelet as a tool for primary prevention. However, the Medic Alert bracelet is less suitable for less acutely emergent situations such as HLA-B*58:01-associated allopurinol HDRs and HLA-B*57:01-associated abacavir HDRs. Sukasem C *et al* [10] have reported successful implementation of the ‘pharmacogenomics card’ in Thailand. The card was issued by a centralized pharmacogenomics laboratory in Bangkok with electronic health record (EHR) properties. Pharmacogenetics findings were provided along with the clinical interpretation of the HLA-B alleles and associated SCAR phenotype for the potentially causative drug. The specific HLA-B risk allele(s) are presented as either ‘negative’ or ‘positive’. ‘Negative’ findings was interpreted as low risk whilst ‘positive’ results were interpreted as high risk of the specific drug induced hypersensitivity reaction phenotype. Both the heterozygous (single copy) and homozygous (double copies) of the genetic variants were collectively reported as ‘positive’. We suggest using the term ‘greater risk’ or ‘lower risk’ for positive and negative results respectively, to signify the range of variably low to moderate PPV as other genetic and/or non-genetic factors may be involved in the pathogenesis of the related HDR.

Despite a number of important pharmacogenetics discoveries with substantial evidence supporting their clinical utility, routine practice and implementation has been slow. In developing countries with limited resources, the first step towards increasing the utilization and implementation of pharmacogenomics data will be the adoption of the EHR with clinical decision support (EHR-CDS) system (Figure 2). Without an effective EHR-CDS system, the results of patients genotyped for HLA-B*15:02 for example, could be lost from the patient’s medical records. This increases the likelihood of developing a hypersensitivity reaction due

to carbamazepine prescription by clinicians, in genetically at-risk individuals. Moreover, it remains challenging for clinicians to recall and apply pharmacogenomics data during clinical practice as increasing numbers of clinically relevant genes are discovered and incorporated into the clinical practice guidelines [11].

For implementation of an EHR-CDS system, an ecosystem adapted from the IGNITE network (Implementing GeNomics In pracTice) is proposed [12]. The IGNITE network suggested establishing a central coordinating center for multiple institutions to evaluate the available evidence and recommendations for specific pharmacogenetics testing besides estimating risk for carriers. However, as a stepping stone we are more inclined to implement this ideal using a single-center approach, as suggested by Manolio TA et al [13], (Supplementary Figure S2).

It remains to be seen whether the proposed Medic Alert bracelet will be an effective tool in the primary prevention against drug hypersensitivity reactions in incidental findings. Pharmacogenomics associations have been well-established in clinically diagnosed HDR subjects. As yet, the application of a similar relationship in subjects without previously reported HDRs to the relevant drug(s) warrants further inter-disciplinary research before its implementation as a screening measure.

Conflict of Interest Statement: All the authors declare no conflict of interest.

Acknowledgements

We would like to thank the Director General of Health Malaysia for his permission to publish this article. We also thank all the subjects who volunteered to participate in this project and, all the clinical and laboratory staff that were involved in this pilot project.

This study was financially supported by Ministry of Health Malaysia: NMRR-16-884-31002/JPP-IMR 16-028.

References

1. Collins SL, Carr DF, Pirmohamed M. Advances in the Pharmacogenomics of Adverse Drug Reactions. *Drug Saf.* 2016 Jan; **39**(1): 15 – 27.
2. Devine EB, Lee CJ, Overby CL, *et al.* Usability Evaluation of Pharmacogenomics Clinical Decision Support Aids and Clinical Knowledge Resources in a Computerized Provider Order Entry System: A Mixed Methods Approach. *Int J Med Inform.* 2014 July; **83**(7): 473 – 483.
3. Pirmohamed M, Ostrov DA, Park BK. New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. *J Allergy Clin Immunol.* 2015 Aug; **136**(2): 236–244.
4. Chang CC, Ng CC, Too CL, *et al.* Association of HLA-B*15:13 and HLA-B*15:02 with phenytoin-induced severe cutaneous adverse reactions in a Malay population. *Pharmacogenomics J.* 2017 Mar; **17**(2):170-173.
5. ACMG. ACMG statement on direct-to-consumer genetic testing. http://www.acmg.net/AM/Template.cfm?Section=Policy_Statements&Template=?CM/ContentDisplay.cfm&ContentID=2975. 2008 April. Accessed 15 June 2018.

- Accepted Article
6. Tan LK, Mohd-Farid B, Salsabil S, *et al.* HLA-A, -B, -C, -DRB1 and -DQB1 alleles and haplotypes in 951 Southeast Asia Malays from Peninsular Malaysia. *Human Immunology*. 2016 October; **77**(10): 818 – 819.
 7. Phillips EJ and Mallal SA. Pharmacogenetics of drug hypersensitivity. *Pharmacogenomics*. 2010 Jul; **11**(7): 973 – 87.
 8. Mallal SA, Phillips EJ, Carosi G, *et al.* HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008 Feb. **358**(6): 568 – 79.
 9. Chang CC, Too CL, Murad S, Hussein SH. Association of HLA-B*1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *Int J Dermatol*. 2011 Feb. **50**(2): 221-4
 10. Sukasem C, Puangpetch A, Medhasi S, Tassaneeyakul W. Pharmacogenomics of drug-induced hypersensitivity reactions: challenges, opportunities and clinical implementation. *Asian Pac J Allergy Immunol*. 2014 June; **32**(2): 111 – 23.
 11. Bell GC, Crews KR, Wilkinson MR, *et al.* Development and use of active clinical decision support for preemptive pharmacogenomics. *J Am Med Inform Assoc*. 2014; **21**: e93 – e99.
 12. Weitzel KW, Alexander M, Bernhardt BA, *et al.* The IGNITE network: a model for genomic medicine implementation and research. *BMC Medical Genomics*. 2016 Jan 5; **9**:1.
 13. Manolio TA, Chisolm RL, Ozenberger B, *et al.* Implementing genomic medicine in the clinic: the future is here. *Genetic Med*. 2013 April; **15**(4): 258 – 67.

Figure legends:

Figure 1. The frequency of different observed HDR-implicated HLA-B alleles in HDRs cases and drug-tolerant controls.

NIUA: Non-steroidal Anti-inflammatory Drugs (NSAIDs) Induced Urticaria Angioedema

HLA: Human Leukocyte Antigen

HDR: Hypersensitivity Drug Reaction

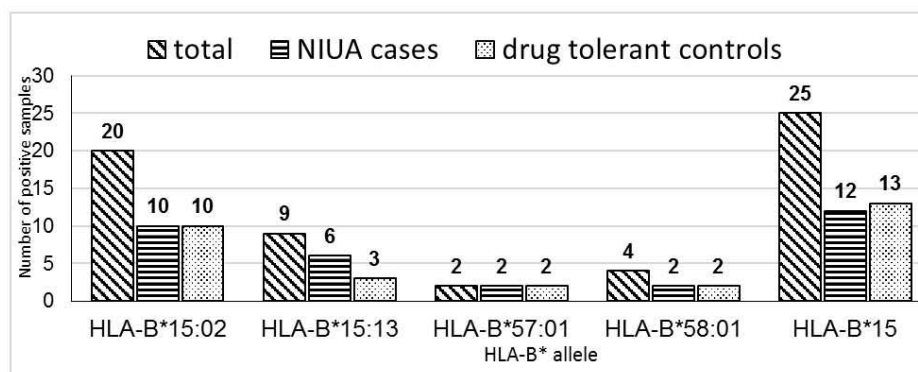


Figure 1. The frequency of different observed HDR-implicated HLA-B alleles in HDRs cases and drug tolerant controls

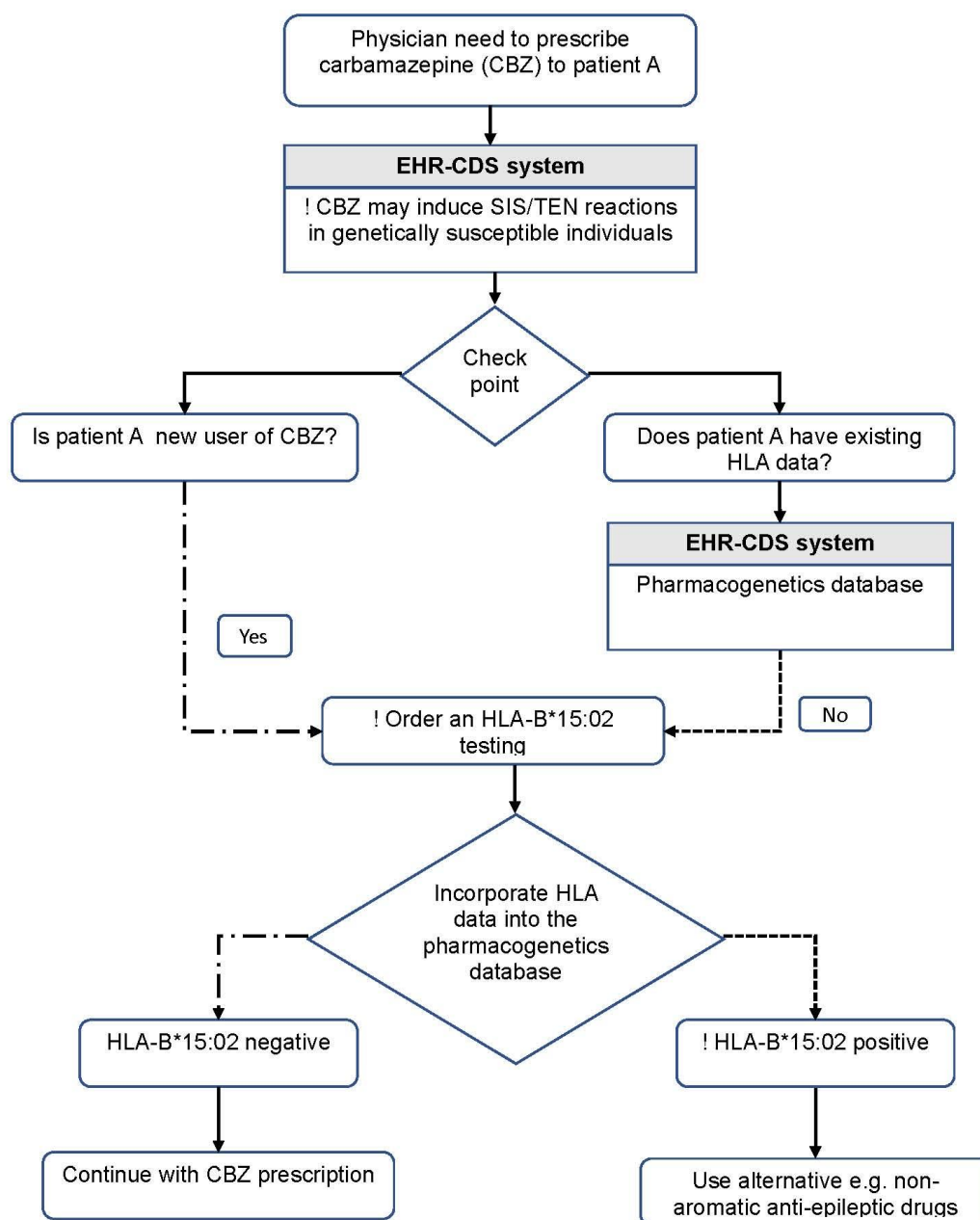


Figure 2. Example of a simple electronic health record (EHR) with clinical decision support system (CDS) used in prescription of carbamazepine. Each arrow signifies a pop-up window for the clinician to make a decision

Supplementary Table S1: Strength of association between various HLA-B alleles and known drug hypersensitivity reactions across different populations

Therapeutic agent	Author, year	Type of adverse drug reaction	Country	Ethnicity	Associated HLA-B alleles	HLA allele positive/ number of patients, %	HLA allele positive/ number of tolerant controls, %	Odds ratios (ORs) range	Reference
Carbamazepine	Kaniwa N et al, 2010	SJS/TEN	Japan	Japanese	B*15:11	14.3	^a		1
	Chang CC et al, 2011	SJS/TEN	Malaysia	Malay	B*15:02	75	15.7 ^b		2
	Hsiao YH et al, 2014	SJS/TEN	Taiwan	Han Chinese	B*15:02	88.4	7.2	4.56-97.62	3
		MPE/DRESS	Taiwan	Han Chinese	B*51:01	24	6.6		3
	Nguyen DV et al, 2015	SCAR	Vietnam	Vietnamese	B*15:02	89.5	24		4
		SJS/TEN /Overlap	Vietnam	Vietnamese	B*15:02	91.4	24		4
Phenytoin	Locharernkul C et al, 2008	SJS	Thailand	Thai	B*15:02	100	0		5
	Cheung YK et al, 2012	SJS/TEN	Hong Kong	Han Chinese	B*15:02	46.7	20		6
	Chung WH et al, 2014	SJS/TEN	Japan, Malaysia	Japanese, Han Chinese	B*15:02	27.1	6.9	3.5-59	7
	Chang CC et al, 2017	SJS/TEN	Malaysia	Malay	B*15:02	61.5	21.9		8
		SJS/TEN DRESS	Malaysia	Malay	B*15:13	53.8	9.4		8
			Malaysia	Malay	B*15:13	100	9.4		8
Allopurinol	Hung SI et al, 2005	SCAR	Taiwan	Han Chinese	B*58:01	100	15		9
	Jung JW et al, 2011	SJS/TEN/AHS	Korea	Korean	B*58:01	100	9.5		10
	Goncalo M et al, 2013	SCAR	Portugal	Cases: Caucasian, Controls: Unspecified	B*58:01	64	4.3	39.1- 580.3	11
	Tohkin M et al, 2013	SJS/TEN	Japan	Japanese	B*58:01	27.8	0.6 ^b		12
	Sukasem et al, 2016	SJS/TEN	Thailand	Thai Chinese/ Siamese	B*58:01	100	4		13
Abacavir	Mallal S et al, 2002	Abacavir Hypersensitivity Reaction	Australia	Caucasian (88%), African (3.5%), Indigenous (5.5%), Asian (3%)	B*57:01	78	2		14
	Saag M et al, 2008	Abacavir Hypersensitivity Reaction	United States	White (54%)	B*57:01	100 ^c	4	117-6934	15
				Black (46%)	B*57:01	100 ^c	1		15
	Berka N et al, 2012	Abacavir Hypersensitivity Reaction	Canada	White (66%), Black (16%), Aboriginal (6%), Other (12%)	B*57:01	100	0.4		16

Abbreviations: OR, odds ratio; CI, confidence interval; ND, not defined; HLA, human leukocyte antigens; SCAR, severe cutaneous adverse reaction; SJS, Steven-Johnson syndrome; TEN, toxic epidermal necrolysis; AHS, allopurinol hypersensitivity syndrome; MPE, maculopapular exanthema; DRESS, drug reaction with eosinophilia and systemic symptoms

- a. Compared with population allele frequency: 0.004-0.008 (Tanaka et al, 1996)
- b. Percentage of HLA-allele positive/ number of general population controls (%)
- c. Patients had immunologically-confirmed hypersensitivity reaction (skin-patch test)

References:

- 1 Kaniwa N, Saito Y, Aihara M, et al. HLA-B*1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia*. 2010; **51**(12):2461–5.
- 2 Chang CC, Too CL, Murad S, Hussein SH; Association of HLA-B*1502 allele with carbamazepine induced toxic epidermal necrolysis and Stevens-Johnson syndrome in the multi-ethnic Malaysian population. *International Journal of Dermatol*. 2011 Feb; **50**(2): 221-224
- 3 Hsiao YH, Hui C-Y R, Wu T, et al. Genotype–phenotype association between HLA and carbamazepine-induced hypersensitivity reactions: Strength and clinical correlations. *Journal of Dermatological Science*. 2014; **73**(2):101-109
- 4 Nguyen DV, Chu HC, Nguyen Doan V, et al. HLA-B*1502 and carbamazepine-induced severe cutaneous adverse drug reactions in Vietnamese. *Asia Pac Allergy*. 2015; **5**:68-77.
- 5 Lochareonkul C, Loplumlert J, Limotai C, et al. Carbamazepine and phenytoin induced Stevens-Johnson syndrome is associated with HLA-B*1502 allele in Thai population. *Epilepsia*. 2008; **49**(12):2087–91
- 6 Cheng YK, Cheng SH, Chan EJM et al. HLA-B alleles associated with severe cutaneous reactions to antiepileptic drugs in Han Chinese. *Epilepsia*. 2013; **54**(7):1307–14.
- 7 Chung W-H, Chang W-C, Lee Y-S, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA*. 2014; **312**(5):525–34.
- 8 Chang CC, Ng CC, Too CL et al. Association of HLA-B*15:13 and HLA-B*15:02 with phenytoin-induced severe cutaneous adverse reactions in a Malay population. *The Pharmacogenomics J*. 2017 Mar; **17**(2):170-173
- 9 Hung SI, Chung WH, Liou LB et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci U S A*. 2005; **102**(11):4134–9.
- 10 Jung J-W, Song W-J, Kim Y-S, et al. HLA-B*58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency, *Nephrol Dial Transplant*. 2011 Nov; **26**(11): 3567–3572
- 11 Goncalo M, Coutinho I, Teixeira V, et al. HLA-B*58:01 is a risk factor for allopurinol-induced DRESS and Stevens-Johnson syndrome/toxic epidermal necrolysis in a Portuguese population. *Br J Dermatol*. 2013; **169**(3): 660–5.
- 12 Tohkin M, Kaniwa N, Saito Y, et al. A whole-genome association study of major determinants for allopurinol-related Stevens–Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *The Pharmacogenomics Journal*. 2013; **13**, 60–69
- 13 Sukasem C, Jantararoungtong T, Kuntawong P, et al. HLA-B*58:01 for Allopurinol-Induced Cutaneous Adverse Drug Reactions: Implication for Clinical Interpretation in Thailand. *Front.Pharmacol*. 2016; **7**:186
- 14 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**(9308):727–32.
- 15 Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008; **46**(7):1111–8.
- 16 Berka N, Gill JM, Liacini A, et al. Human leukocyte antigen (HLA) and pharmacogenetics: screening for HLA-B*57:01 among human immunodeficiency virus-positive patients from southern Alberta. *Hum Immunol*. 2012; **73**(2):164–7.

Supplementary Table S2. The demographic and clinical characteristics of studied subjects (n = 68)

Characteristics	Cases (n=35)	Tolerant controls (n=33)
Age (mean $\pm$ SD)	31.0 $\pm$ 10.2	34.7 $\pm$ 8.0
Gender (male/female)	9/26	10/23
Ethnicity	Malay	Malay
Atopy* (%)	62.9%	21.2%
Underlying chronic disease† (%)		
i) Ischaemic heart disease	2.9%	0
ii) Hypertension	5.7%	12.1%
Previous drug exposures‡:		
i) β -lactam antibiotics (%)	100%	100%
ii) $\geq$ 2 chemically different NSAIDs group (%)	100%	100%

SD, standard deviation

*In this study, atopy was defined as the presence of at least grade III specific IgE to at least one of the common local aeroallergens and/or food allergens in the presence of personal history of allergic rhinoconjunctivitis and/or atopic dermatitis and/or asthma.

† All subjects did not have chronic spontaneous urticaria, chronic active thyroid disease with/without thyroid antibodies, autoimmune diseases with/without positive antinuclear antibodies, nasal polyposis, chronic kidney disease and/or cancer.

‡ All subjects have not been exposed to abacavir, allopurinol, carbamazepine and phenytoin prior to recruitment.

Supplementary Table S3. The NPV, PPV and number needed to test to prevent one case of drug hypersensitivity or related syndromes in the Malay population

Drug	HLA Allele	Malay HLA carriage rate	HDR phenotype	Negative predictive value (NPV)	Positive predictive value (PPV)	Number needed to test (NNT) to prevent '1'	Reference
Carbamazepine	B*15:02	12.1%†	SJS/TEN	98.4%	20.3%	1333	Chang CC et al [4]
Phenytoin	B*15:13	6.0%†	SJS/TEN	97.1%	16.3%	1851	Chang CC et al [9]
Abacavir (ABC)	B*57:01	1.1%†	ABC hypersensitivity	100%‡	76.7%‡	13‡	Phillips EJ & Mallal SA [7]
Allopurinol	B*58:01	5.8%†	SJS/TEN or DRESS	100%‡	2.7%‡	250‡	Phillips EJ & Mallal SA [7]

† Data derived from article published by *Tan LK et al* [6].

‡We assumed that the genetic effects of HLA-B*57:01 and B*58:01 on abacavir and allopurinol respectively could be generalized to multiple ethnic population (*Mallal SA, Phillips EJ, Carosi G, et al* [8] and *Phillips EJ and Mallal SA* [7] respectively).

The calculation of NPV, PPV and NNT for carbamazepine and phenytoin were based on the formula used by *Phillips EJ and Mallal SA* [7]. The calculation of NPV was based on the Malay normal controls.



Yayasan MedicAlert® Malaysia
(MedicAlert® Foundation Malaysia)

101 Menara Mutiara Majestic, 15 Jalan Othman,
46000 Petaling Jaya, Selangor Darul Ehsan, Malaysia
Tel/ Fax: +603 7782 0515 Hotline: +6012 3411137
www.medicalert.com.my

MEMBERSHIP APPLICATION & REGISTRATION FORM

To be completed by applicant and doctor.
Please mail to: **MedicAlert® Foundation Malaysia**
Or email to: **medicalertmalaysia@gmail.com**

Please [✓] tick appropriate box.

- ☐ New Membership ☐ Renewal
☐ Replacement ☐ Update Membership Information

MEMBER'S DETAILS

Full Name: I/C No:
Sex: (Male / Female) Ethnic: Nationality: Date of Birth:
Mailing Address:
..... Postcode:
Occupation:
Phone (Home): (Mobile): (Office):
(Fax): Email Address:

NEXT OF KIN DETAILS

Full Name: I/C No:
Ethnic: Relationship:
Address:
..... Postcode:
Phone (Home): (Mobile): (Office):
(Fax):

DOCTOR'S DETAILS

Doctor's Name: Hospital/Clinic Name:
Address:
..... Postcode:
Phone (Office): (Mobile): (Fax):

MEDICAL CONDITIONS (PLEASE TICK APPROPRIATELY, WILL BE ENGRAVED)

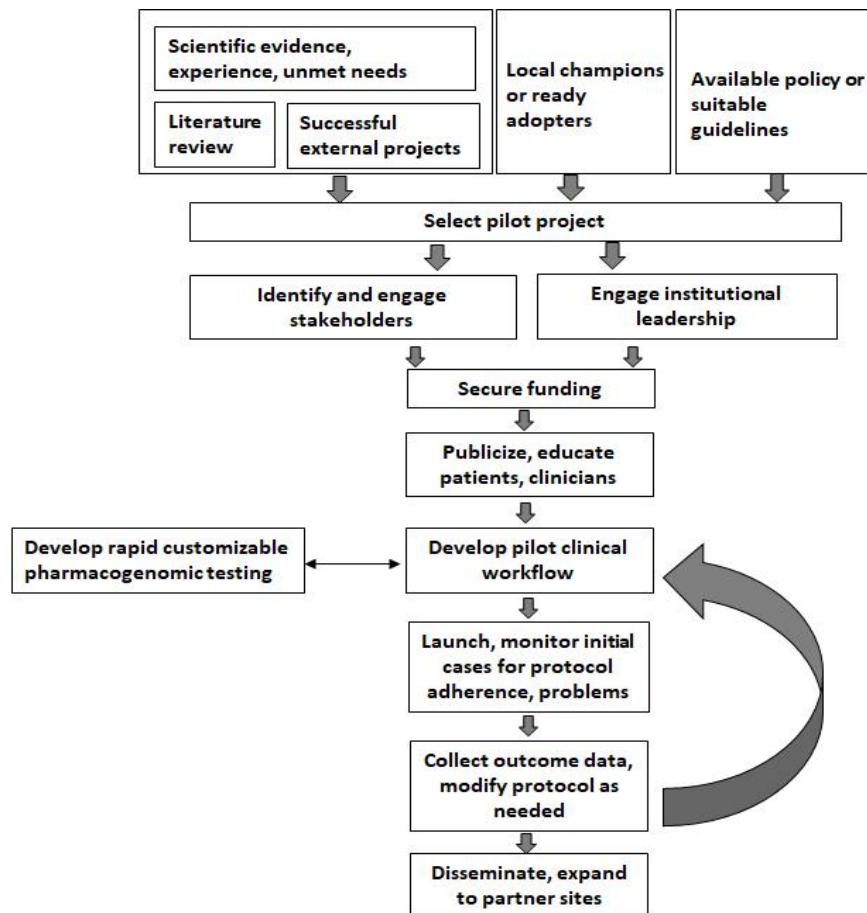
- | | | |
|---|---|--|
| ☐ Angina | ☐ Emphysema | ☐ Hypothyroidism |
| ☐ Arthritis | ☐ Epilepsy | ☐ Immunosuppressed |
| ☐ Asthma | ☐ Glaucoma | ☐ Myocardial Infarction |
| ☐ Atrial Fibrillation | ☐ Hearing Impairment | ☐ Nephropathy |
| ☐ Chronic Obstructive Pulmonary Disease (COPD) | ☐ Hemodialysis | ☐ Neuropathy |
| ☐ Congestive Heart Failure | ☐ Hypercholesterolemia | ☐ Retinopathy |
| ☐ Coronary Artery Disease | ☐ Hypertension | ☐ Seizure Disorder |
| ☐ Diabetes | ☐ Hypoglycemia | ☐ Stroke |
| ☐ Others (please specify) <input type="text"/> | | |

MedicAlert® Foundation Malaysia is a nonprofit organization registered with the Registrar of Societies with Registration Number 194 (Selangor) pursuant to the Societies Act 1961.
MedicAlert® Foundation Malaysia relies on contributions to support our 24/7 emergency centre and our professional education efforts.

MEDICAL DETAILS (PLEASE TICK APPROPRIATELY, WILL BE ENGRAVED)			
ALLERGIES	MEDICATIONS		BLOOD GROUP
☐ Aspirin ☐ Barbiturates ☐ Codeine ☐ Demerol ☐ Iodine ☐ Latex ☐ Lidocaine ☐ Morphine ☐ Novocaine ☐ Penicillin ☐ Sulfa ☐ Tetracycline ☐ X-Ray Dyes ☐ No known allergies ☐ Others (please specify)	☐ Amaryl ☐ Aspirin ☐ Atenolol ☐ Coumadin ☐ Digoxin ☐ Enalapril Maleate ☐ Furosemide ☐ Gemfibrozil ☐ Glipizide ☐ Glyburide ☐ Hydrochlorothiazide ☐ Insulin (type and dosage)	☐ Isosorbide Mononitrate ☐ Lisinopril ☐ Metformin ☐ Metoprolol ☐ Plavex ☐ Potassium Chloride ☐ Ranitidine ☐ Triamterene/HCTZ ☐ Others (please specify)	☐ A ☐ B ☐ AB ☐ O ☐ Rhesus ☐ +ve ☐ -ve
Details of Adverse Reactions and Additional Medical Information			
By accepting membership in MedicAlert® Foundation Malaysia, I authorize MedicAlert to release all medical and other confidential information about me, in emergencies, to other healthcare personnel. MedicAlert relies upon the accuracy of the information members supply. Member therefore agrees to defend, indemnify and hold MedicAlert (including its employee, officers and agents) harmless from any claim or lawsuit brought by member or others for injury, death, loss or damages arising in whole or in part out of member's provision of incomplete or inaccurate information to MedicAlert. I agree that the facts as stated are correct to the best of my knowledge. <i>(kindly stamp doctor's chop here)</i>			
Signature: (Applicant) (A parent or guardian signature is required for those under the age of 18).		Signature: (Doctor)	
Guardian Name		Guardian I/C No.	Guardian Relationship
Please tick [✓] the choice of emblem required: ☐ Neck Pendant ☐ Wrist Bracelet <i>Basic emblem cost RM 50 each</i>   <i>Pictures shown above are for illustration purposes only</i>		FOR OFFICE USE ONLY Registration Date: Registration No:/...../MAL Cash/PO/Cheque Payment Ref#: Process Date: Processed By: Membership Expiry Date: "Protecting and Saving Lives"	

MedicAlert Application Form (October 2013)

Supplementary Figure S1. Sample of the locally utilized medic alert bracelet form



Supplementary Figure S2. Initial implementation roadmap of pharmacogenetics data at a single institution with subsequent evaluation and their ultimate dissemination (Adapted and modified from Manolio et al⁹, with permission).