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RESEARCH LETTER

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Incidental pharmacogenetics findings in an HLA-related research: Considerations for primary prevention

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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, that is exanthem, urticaria and angioedema to the critical, that is 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 includes Her2/neu testing for metastatic breast cancer patients to determine responsiveness to Herceptin® and the use of thiopurine 6-mercaptopurine testing to manage the treatment of children with acute lymphoblastic leukaemia.[2] Several genetic studies have demonstrated that certain human leucocyte 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] (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 are presented in 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 (Figure S1) notification and registration form were 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 whilst 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 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

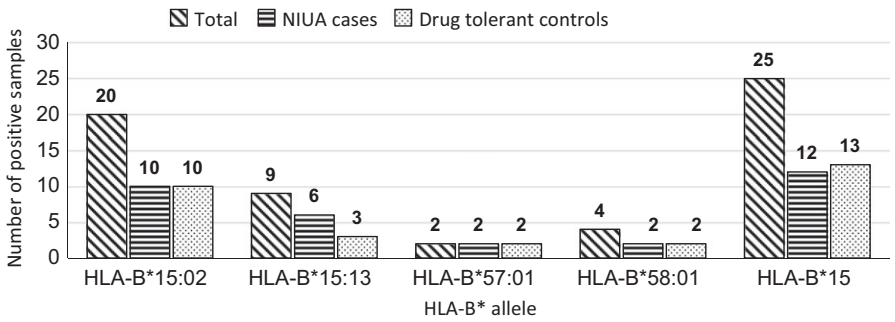

FIGURE 1 The frequency of different observed HDR-implicated HLA-B alleles in HDRs cases and drug-tolerant controls. HDR, hypersensitivity drug reaction; HLA, human leucocyte antigen; NIUA, Non-steroidal anti-inflammatory drug (NSAID)-induced urticaria angioedema

abacavir HDRs. Sukasem et al[6] 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 were 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 have 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.[7]

For implementation of an EHR-CDS system, an ecosystem adapted from the IGNITE network (Implementing GeNomics In practicE) is proposed.[8] The IGNITE network suggested establishing a central co-ordinating 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,[9] (Figure S2).

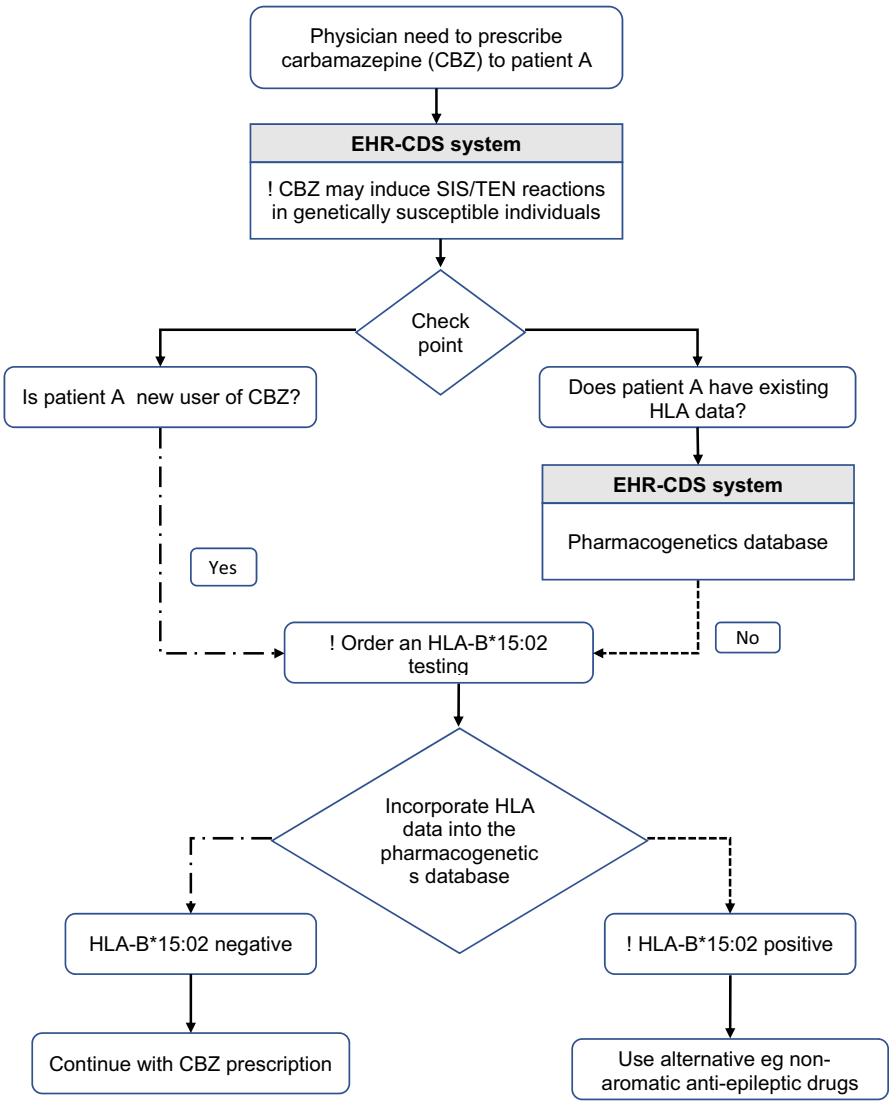

FIGURE 2 Example of a simple electronic health record (EHR) with clinical decision support system (CDS) used in prescription of carbamazepine. Each arrow signifies a pop-up window for the clinician to make a decision

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 interdisciplinary research before its implementation as a screening measure.

AUTHOR CONTRIBUTION

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

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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