

Pharmacogenetics and its Relevance to Clinical Practice

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Introduction

Pharmacogenetics is aimed at elucidating the influence of genetic variations on drug response. Genetic variations, of which single-nucleotide polymorphisms are the most common, can affect gene expression and thereby cause alterations in protein expression level, structure and function. Thus, functional polymorphisms in drug metabolising enzymes, transporters and targets can potentially alter the pharmacokinetics and pharmacodynamics of drugs.¹ It should therefore come as no surprise that these variations have been shown to contribute substantially to the inter-individual variability in drug efficacy and toxicity that plagues current clinical practice. The promise of pharmacogenetics thus lies in its potential to identify clinically significant genetic variations that can account for phenotypic variations in drug response and, in so doing, enable genotype-guided optimisation of pharmacotherapy and drive the paradigm shift towards personalised medicine.

Drug-specific Clinical Applications of Pharmacogenetics

Irinotecan

A critical aspect of this evolving paradigm is the heterogeneity in therapeutic outcomes to drugs that are ethnic-dependent. Irinotecan is a case in point. Variants of the *UGT1A1* gene, *UGT1A1**28 and *UGT1A1**6, have

been associated with impaired glucuronidation and higher plasma levels of the active metabolite of irinotecan, SN-38, in patients receiving standard doses of irinotecan.² The *UGT1A1* genotype has since been demonstrated to be predictive of irinotecan-induced toxicities, particularly severe neutropenia and diarrhoea.³

Interestingly, there exist inter-ethnic differences in the frequency distribution of the *UGT1A1**28 and *UGT1A1**6 alleles, with the *UGT1A1**6 polymorphism being completely absent in Caucasians (Figs. 1A and 1B). Our studies have also shown that the local prevalence of the *UGT1A1**6 allele was approximately 3 to 5 fold higher in Chinese than in the Malay and Indian populations and that patients homozygous for the *UGT1A1**6 allele had at least 2-fold higher levels of SN-38 compared to patients carrying wild-type alleles, and were more likely to experience severe neutropenia.⁴ These findings have led to a change in the local package inserts for irinotecan by the Health Sciences Authority (HSA) to highlight and mitigate the risk of severe toxicities in patients receiving irinotecan who are carriers of at least one of these alleles.⁵

A prospective National Medical Research Council (NMRC)-funded phase I trial of genotype-based dosing of irinotecan is currently on-going at the National Cancer Centre Singapore (NMRC/1197/2008). We have already

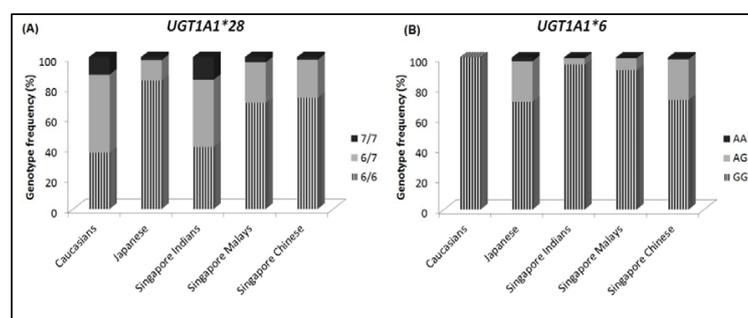


Fig. 1. (A) Genotype distribution of *UGT1A1**28. (B) Genotype distribution of *UGT1A1**6. (Adapted from Jada et al, 2007.⁴)

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determined the dose of irinotecan to be 100 mg/m² in patients who are either wild-type at both loci or wild-type at one locus and heterozygous at the other locus or heterozygous at both loci. Patients harbouring these genotype statuses rarely experienced diarrhoea or neutropenia greater than grade 1 in severity. Recruitment is ongoing to determine the dose of irinotecan in patients with wild-type genotype at one locus and homozygous variant genotype at the second locus.

Carbamazepine

Screening for *HLA-B*1502* before initiating carbamazepine therapy is another example of the clinical significance of pharmacogenetics. The strong association between *HLA-B*1502* carriage and the risk of carbamazepine-induced Stevens Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) has been supported by local and international data.⁶ Of note, the frequency distribution of this allele shows a distinct regional and ethnic pattern, with its prevalence being the highest among Asians (1% to 10%) and much lower among Europeans (0 to 0.02%) and certain subsets of Asians, including the Japanese (0.1%) and Korean (0.5%).⁷ In view of its high prevalence locally, screening for this allele prior to initiation of carbamazepine therapy is now recommended as standard of care by the Ministry of Health (MOH) and drug labelling changes have been implemented by the HSA.

More recently, *HLA-A*3101* has also been associated with an even broader range of carbamazepine-induced hypersensitivity reactions, including mild maculopapular exanthema, hypersensitivity syndrome and SJS/TEN.⁸ The higher frequency of *HLA-A*3101* allele,⁸ in contrast to *HLA-B*1502*, in many different populations has raised the question of whether the screening for *HLA-A*3101* may be of greater clinical utility since it may be applicable to more populations. However, this remains to be elucidated.

Clopidogrel

As a pro-drug, clopidogrel undergoes metabolic activation to its pharmacologically active thiol metabolite, which then exerts its antiplatelet effects through the irreversible inhibition of the P2Y₁₂ ADP receptor (Fig. 2). The presence of *CYP2C19* loss-of-function alleles, *CYP2C19*2* and *CYP2C19*3*, has been associated with lower plasma levels of the active thiol metabolites and significantly higher risks of major adverse cardiovascular events and stent thrombosis.⁹ In contrast, the gain-of-function allele, *CYP2C19*17*, has been associated with enhanced antiplatelet effects and higher risks of bleeding.⁹ The mounting evidence in the literature has prompted the United States' Food and Drug Administration (FDA) to include a boxed warning on clopidogrel label describing these associations.

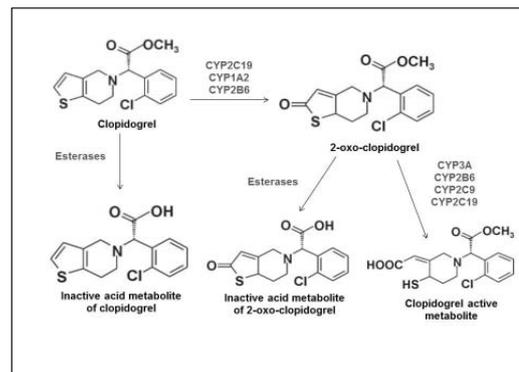


Fig. 2. Metabolic pathway of clopidogrel. (Adapted from Farid et al, 2010.¹⁰)

To date, HSA has not implemented a labelling change for clopidogrel locally, perhaps because information regarding the influence of these polymorphisms on clopidogrel pharmacokinetics and pharmacodynamics is currently lacking in our local population. Given the marked variation in allelic frequencies of *CYP2C19*2*, *CYP2C19*3* and *CYP2C19*17* among the different local ethnic groups, ethnic variability in clopidogrel response should be anticipated and the results of a study investigating the significance of that genetic association in the local context will be of great interest and may eventually aid in the personalisation of clopidogrel therapy in our population.

Challenges and Future Directions in the Clinical Implementation of Pharmacogenetics

While pharmacogenetics findings have the tremendous potential to optimise therapeutic outcomes, there are caveats to their clinical implementation that need to be addressed. Firstly, most pharmacogenetics studies to date have utilised the candidate gene approach. These have uncovered a significant source of variability in drug response but most drug responses are likely to be polygenic. The candidate gene approach also relies heavily on prior knowledge of drug pharmacology and traits of interest. For these reasons and parallel to the remarkable advances made in sequencing technologies, there has been a steady shift from pharmacogenetics to pharmacogenomics, which encompasses a much broader approach since the focus is shifted from one or a few single genes in a single chromosome to the genes in all chromosomes. Large scale efforts in whole genome sequencing, such as genome-wide associated studies, have identified loci that are essential for determining genotype-phenotype associations, and this approach is expected to reveal novel pathways and more clinically significant associations in years to come.

In addition, since inter-individual variability is a multi-faceted issue that implicates more than just one factor, personalised medicine can only be achieved through

concerted efforts and close collaborations between multiple groups in multiple disciplines. Other approaches, including proteomics, transcriptomics, metabolomics and bioinformatics, will be essential in the elucidation of all the relevant factors influencing drug response, and the integration of knowledge gathered from all these approaches will be of paramount importance. In a recent study by Roychowdhury et al,¹¹ high throughput whole-genome sequencing and transcriptomics were applied in clinical oncology which led to the identification of informative mutational landscapes specific to individual patients that could inform rational combination of therapies to optimise efficacy and minimise the risks of resistance. This study was only a pilot study involving 2 patients with advanced cancers but perhaps this is the direction that we need to move towards in the pursuit of personalised medicine.

Moving forward, the clinical implementation of pharmacogenetics and pharmacogenomics findings would necessitate a comprehensive understanding of pharmacogenetics principles and their relationships to the pharmacokinetics and pharmacodynamics of drugs among clinicians, pharmacists and other healthcare professionals, which is currently lacking. Training in how to interpret and apply this knowledge in relation to other clinical variables needs to be incorporated into the curriculum of medical and pharmacy schools. Equally important will be the simultaneous research efforts that are geared towards understanding the relevance of genotype-drug response associations in the diverse ethnic groups in our local population. This would require the establishment of proper infrastructures and close local, regional and international collaborations.

The goal of personalised medicine is the delivery of the most appropriate drug at an optimal regimen that would maximise therapeutic efficacy and minimise toxicity for an individual patient. Although there have been a few successful examples, the clinical translation of most pharmacogenetics information remains complex and challenging. It is still premature to gauge the clinical implications of pharmacogenetics and pharmacogenomics because many aspects are still docked with unresolved challenges but these approaches are anticipated to yield many clinically actionable findings that will ultimately pave the way for personalised medicine.

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