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A minireview of *CYP2C9* and *CYP2C19* single nucleotide polymorphisms (SNPs) among Malaysian populations

***Abstract*—** It has been recognized extensively that studies of pharmacogenetics provide massive examples of causal relationship between genotypes and drug effectiveness to account for interindividual phenotypic variations in drug therapy. In most cases, cytochrome P450 (CYP) polymorphisms are one of the major variables that affecting those drug plasma concentration, drug detoxification and drug activation in humans. Thus, understanding of CYP polymorphisms can be crucially valuable in order to allow early and more accurate drug dosage prediction and improve the drug response accordingly. Despite the high level of homologous amino acid sequences, *CYP2C9* and *CYP2C19* genes are among the most important CYP genes which metabolize a wide range of clinically therapeutic drugs. Several critical reviews have been published relating to the aforementioned genes. However, this minireview aims to systematically merge reported studies on the SNPs frequencies of both genes concentrating only on Malaysian population. It is hoped that, the minireview can be an opener for new opportunities to reevaluate the evidence on the prevalence of CYP2C genes as a potential genetic factor influencing a particular drug efficacy and safety among Malaysian. Such evaluation can be developed to the next level of early prediction of better and specific drug treatment, thereby improving the drug response while helping the government in minimising the drug expenditures.

***Keywords*— pharmacogenetics, cytochrome P450, *CYP2C9* gene, *CYP2C19* gene, Malaysian population, allele frequency, personalized medicine**

1 INTRODUCTION

Population pharmacogenetics study provides a broad opportunity for comprehensive understanding of molecular basis, mechanisms in drug efficacy and toxicity based on the polymorphism characteristics in different people. The variability of the underlying genes which involve whether in absorption, metabolism and elimination or via pharmacodynamics, are thought to bring pharmacological differences at personal level or among the population groups [1]. There are several kinds of genes responsible for distinctions in drug metabolism and response where the genes of CYP are among the most common. The diverse endogenous functions and critical roles of CYP genes explain the importance of the enzymes to human medications [2].

In human, CYP is a superfamily of hemoproteins involved primarily in catalysing the detoxification processes. The genes encode the CYP class of metabolic enzymes which can be found and expressed mostly in the liver and intestines.

Conforming to an evolutionary scheme, a standardized system of nomenclature has been curated to name and assign individual genes into families and subfamilies of CYP. It is based on the level of amino acid sequence identity, phylogenetic association and gene organization as determined by the Cytochrome P450 Homepage (http://drnelson.uthsc.edu/cytochrome P450.html). The basis for all CYP genomic and complementary DNA (cDNA) sequence names is an italicized 'CYP'. The individual family is then

designated by an Arabic numeral and the subfamily with a letter. Member sequences within a subfamily are numbered consecutively. The gene and the allele name are separated by an asterisk followed by Arabic numerals designating the specific allele as it is reported to the nomenclature committee. The examples of how the CYP genes were described can be seen in Table I. Likewise, the same nomenclature is used for mRNA and protein sequences except that the designations are not italicized.

Table I: Examples of how the nomenclature of CYP Genes were designated

Class	*CYP3A4*21*	*CYP2C9*7*	*CYP2C19*3*[a]
Genetic superfamily	CYP	CYP	CYP
Genetic family	3	2	2
Genetic subfamily	A	C	C
Specific gene	4	9	19
*allele	21	7	3

A standard system of CYP nomenclature for gene and cDNA is determined by the Cytochrome P450 Homepage (http://drnelson. uthsc.edu/cytochromeP450.html). The same nomenclature is also applied for mRNA and protein sequences except the designations are not italicized.

The CYP SNPs of human beings are summarized in the Human Cytochrome P450 Allele Nomenclature Database home page (www.cypalleles.ki.se) present on a server at Karolinska Institute, Sweden. To date, it encodes at least 58 CYP genes and 29 pseudogenes where they have been organized into 18 families and 43 subfamilies. The CYP SNPs may involve of nucleotide substitution, insertion, deletion or duplication. As a result, it causes the change of substrate specificity, for example the sequence of amino acid, the exhibition of premature stop codon or splicing defect. This involves not only in the open reading frame with respect to modify the function of the genes, but also in the intronic regions.

Based on the CYP homepage mentioned, it appears that *CYP2D6*, *CYP2C9* and *CYP2C19* are the three genes which have attracted the most attention among researchers worldwide [3]. The most abundant of CYP enzyme content in human liver are CYP3A4 (~28%), followed by CYP2C family (18%) and CYP1A2 (~12%). However, the most currently involved genes in metabolizing clinical drugs are *CYP3A4* (51%), followed by *CYP2D6* (24%) and the CYP2C subfamily genes (~20%) [4]. Some CYP genes are also highly polymorphic for instances *CYP2D6*, *CYP2C9*, *CYP2C19* and *CYP3A4*. Due to variability of enzyme activities rendering from the functional polymorphic CYP genes, the drug-metabolizing phenotype of oneself can be characterized to ultrarapid metabolizer (UM), extensive metabolizer (EM), intermediate metabolizer (IM) and poor metabolizer (PM).

CYP2 is known as the largest family of CYP genes in human encompassing approximately one third of total CYPs sequences and 13 subfamilies, including the CYP2C's [5]. Located in chromosome 10q23.33, there are four genes identified in CYP2C subfamily; *CYP2C8*, *CYP2C9*, *CYP2C18* and *CYP2C19* [6] (Figure 1). The CYP2C genes encode proteins that accounts for over 20-30% of the total liver CYP content [7]. The CYP2C enzymes were also the first among CYP enzymes to be purified from human tissues [5]. Particularly, the most clinically important genes in the CYP2C subfamily are *CYP2C9*, *CYP2C19* and *CYP2C8*. The genes are estimated to be 20% responsible in metabolizing clinically administered drugs and endogenous compounds such as arachidonic acid (AA). They share more than 82% of identical amino acid sequences in the region [8]. However, the expressed product from *CYP2C9* and *CYP2C19* genes, CYP2C9 and CYP2C19, are showing 92% homology, differing by only 43 over 490 amino acids in the sequence [9]. These two genes are also primarily involved with xenobiotic metabolism [10].

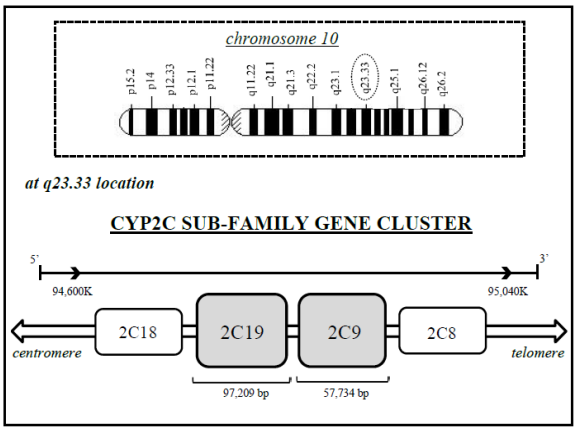

Figure 1. The sequence of *CYP2C9* and *CYP2C19* genes in chromosome 10. The *CYP2C9* and *CYP2C19* genes are mapped to the long arm (q) of chromosome 10 at position 23.33. The human CYP2C subfamily consists of four isoforms where *CYP2C9* and *CYP2C19* are the most important genes for drug metabolism from this subfamily.

2 *CYP2C9* GENE

The *CYP2C9* gene (NCBI ref: NG_008385.1) is located in chromosomal region 10q23.33 and contains nine exons in the sequence [8]. It constitutes 50% of isozymes from the CYP2C subfamily members and juxtaposes by the *CYP2C19* and *CYP2C8* genes in the region [11]. With the size of almost 58kbp, the gene encodes a protein of 490 amino acid residues [6]. Thus far, 57 allelic variants of *CYP2C9* gene have been detected mostly in the regulatory and coding regions. The *CYP2C9* is commonly expressed in the liver where it involves in the oxidation of a wide range of drugs including S-warfarin, phenytoin, losartan, tolbutamide and torasemide. Several nonsteroidal antiinflammatory drugs (NSAIDs) namely diclofenac, naproxen, ibuprofen and piroxicam, as well as the selective COX-2 inhibitor celecoxib, are also mainly metabolized by CYP2C9 [12]. The expression level of CYP2C9 is the highest among CYP2C enzymes and representing ~20% from the hepatic content. There are only two amino acid substitutions recognized as the most common SNPs in *CYP2C9* gene; *CYP2C9*2* and *CYP2C9*3*. Both SNPs were reported to be majorly responsible in the decrement of CYP2C9 activities in the body. *CYP2C9*2* is formed by a C430T substitution in exon 3 which leads to Arg144Cys conversion whereby the *CYP2C9*3* is due to a C1075T in exon 7, resulting to an altered protein of Ile359Leu substitution. Other than these two, to date, there are about 54 rare SNPs identified in *CYP2C9* gene in human such as *CYP2C9*4*, *CYP2C9*5*, *CYP2C9*11* and *CYP2C9*27*.

In Malaysia, the *CYP2C9*2* allelic frequency among Malay was less than 1.9%, according to Table II. This was significantly lower than the frequency reported among Indian (2.1 – 5.0%). Meanwhile, none of the Chinese appeared to be the allele carrier of the SNP as described in all studies [13,14,15]. Interestingly, the similar pattern can also be seen among Japanese, Chinese from mainland China and Korean [16,17,18]. For common *CYP2C9*3* allelic frequency of 36.2%, it was found to be tremendously high in Jahai tribe, the aboriginal people in Malaysia and differed significantly among other Malaysian ethnic groups [19]. This made the Jahais as the highest *CYP2C9*3* allele carriers among other populations in Southeast Asia (SEA) reported thus far. The frequency of *CYP2C9*3* in three major ethnic populations demonstrated various trends where Indian derived the highest frequency (9.0 – 10.0%) and Malay with the lowest frequency (1.0 – 3.9%). While in the Chinese, the SNP frequency was between 2.4% to 5.0%. Two rare missense polymorphisms (*CYP2C9*4* and *CYP2C9*5*) investigated among ethnic groups in Malaysia were completely absent. The unique *CYP2C9*4* allele frequency was first detected in 1 of 32 Japanese patients with epilepsy and among Lebanese population (1.0%), eventually, after more than a decade of its discovery [20,21]. Meanwhile, it has been suggested that *CYP2C9*5* polymorphism is the exclusive SNP which can only be found in people of African origin [22,23]. To date, no other ethnic group in the world was documented to be the carrier of the SNP.

Table II: The reported *CYP2C9* SNPs allelic frequencies among Malaysian populations

Ethnic groups (*n*)	Allelic Frequency (%)					Ref
	*1	*2	*3	*4	*5	
Malay (183)	96.0	1.0	3.0	0.0	0.0	[19]
Jahai (155)	63.8	0.0	36.2	0.0	0.0	
Malay (76)	99.0	0.0	1.0	nd	nd	[13]^
Chinese (76)	95.0	0.0	5.0	nd	nd	
Indian (76)	88.0	3.0	9.0	nd	nd	
Malay (202)	95.7	1.9	2.4	0.0	0.0	[14]
Chinese (165)	97.3	0.0	2.4	0.0	0.0	
Indian (165)	88.2	2.1	9.7	0.0	0.0	
Malay (51)	96.1	0.0	3.9	nd	nd	[15]*
Chinese (50)	97.0	0.0	3.0	nd	nd	
Indian (50)	85.0	5.0	10.0	nd	nd	

**1* is encoded for *CYP2C9*1* as wild type variant;- assigned in absence of other detectable variants alleles. *2, *3, *4 and *5 are *CYP2C9*2*, *CYP2C9*3*, *CYP2C9*4* and *CYP2C9*5* accordingly. Abbreviation: (*n*) = (number of subjects), nd = not determined in the respective study, ^ = study done on Singaporean populations, * = only healthy groups were considered.

3 *CYP2C19* GENE

CYP2C19 gene (NCBI ref: NG_008384.2) is one of the most highly polymorphic CYP genes spanning nine exons in the region. The size is around 90kbp and is located in chromosome 10q23.33 which produces a protein of 490 amino acids. The gene is one of five major CYP genes which play the most crucial role in drug metabolism, accounting for 8-10% of the drug metabolizing process [24]. The ability of CYP2C19 to metabolize a number of common and important prescription drugs such as

anticonvulsant, antidepressant, antiplatelet, antimalarial, antithrombotic, antiretroviral or antifungal, antiulcer, beta blocker and proton pump inhibitor, does markedly affect the therapeutic level of the drugs respectively. It also plays role as an inhibitor to the compounds of fluvoxamine, pantoprazole, lansoprazole and ticlopidine but acts an inducer for compounds such as phenobarbital and rifampin [25]. Owing to its importance, like the 'twin', the *CYP2C9* gene, it has now been the focus in some pharmacogenetics researches; to the extent that SNPs in the gene are part of FDA-approved diagnostic tools [26].

About 24 mutant allelic variants of *CYP2C19* gene were discovered till today where *CYP2C19*2*, *CYP2C19*3* and *CYP2C19*17* alleles showing evidence to be the most clinically important SNPs in drug administration. *CYP2C19*2* (G681A) alters the reading frame of mRNA from amino acid 215 producing a stop codon 20 bp downstream where this creates a truncated protein (Pro227-) in exon 5 [8]. Consisting of a G636A in exon 4, *CYP2C19*3* leads to an amino acid change of Trp212Ter and creates a premature stop codon with truncated proteins. While for *CYP2C19*17* (Ile331Val), it is characterized by C−806T conversion in the promoter region of the *CYP2C19* gene. If a person possess either one or both of *CYP2C19*2* and *CYP2C19*3* polymorphisms, the drug metabolism may associate with higher toxic concentration or therapeutic failure when treated with normal dosage. In the meantime, *CYP2C19*17* allele has been reported to cause an increment in the rate of transcriptional pathway leading to the growth of the enzymatic activity and rapid drug metabolism [27]. Other instances of *CYP2C19* SNPs detected among human are *CYP2C19*9*, *CYP2C19*13*, *CYP2C19*14* and *CYP2C19*18*.

The Han Chinese were revealed to have the *CYP2C19*2* allelic frequency with 33.1% [28]. This data is relatively comparable with Malaysian Chinese who were in the range between 31.0 – 36.8%, based on the Table III. In contrast, Malay showed significantly lower frequency of the SNP (23.0 – 27.6%) compared to the Chinese. However, Indian ethnic group carried the highest SNP allelic frequency with 38.0% while the aboriginal ethnics of Peninsular Malaysia had the significantly least of *CYP2C19*2* allele frequency which was lower than 10.3%. Furthermore, 5.0% to 10.3% of Malays and less than 1.0% of Indians were the *CYP2C19*3* allele carriers. On the contrary, the Chinese population had shown various statistically significant differences of this loss-of-function allele frequency in all studies (2.6% in a study by Mejin [29], 7.0% in a study by Lim [13] and 10.0% in a study by Seng [15]). For the aboriginal people, though they are classified as a group of native ethnic, Negrito and Senoi derived statistically significant difference in *CYP2C19*3* allelic frequency (1.7% versus 13%). In the meantime, all major ethnic groups in the region are considerably very little carrying the allele of gain-of-function *CYP2C19*17*, except in Indian with almost 20% of them exhibited minimum one allele of the SNP. While for the rare polymorphism *CYP2C19*35*, 16.7% and 1.7% of Proto-Malay and Negrito were found to be the carrier of the SNP respectively. Nonetheless, other reported studies of *CYP2C19* polymorphisms in Malaysia and Singapore did not determined the allelic frequency of this rare SNP.

Table III: The reported *CYP2C19* SNPs allelic frequencies among Malaysian populations

Ethnic groups (*n*)	Allelic Frequency (%) *1	*2	*3	*17	*35	Ref
Negrito (29)	79.4	6.9	1.7	10.3	1.7	(30)*
Senoi (27)	81.4	5.6	13.0	0.0	0.0	
Proto-Malay (60)	83.3	0.0	0.0	0.0	16.7	
Malay (29)	60.4	27.6	10.3	1.7	nd	(29)
Chinese (57)	58.8	36.8	2.6	1.8	nd	
Iban (24)	70.8	16.7	10.4	2.1	nd	
Other (8)	62.7	6.0	6.3	25.0	nd	
Malay (76)	40.0	23.0	7.0	5.0	nd	(13)^
Chinese (76)	60.0	32.0	7.0	1.0	nd	
Indian (76)	42.0	38.0	1.0	19.0	nd	
Malay (54)	72.0	23.0	5.0	nd	nd	(31)
Chinese (68)	59.0	31.0	5.0	nd	nd	
Indian (20)	63.0	38.0	10.0	nd	nd	

**1* is encoded for *CYP2C19*1* as wild type;- assigned in absence of other detectable variants alleles. **2*, **3*, **17* and **35* are *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17* and *CYP2C19*35* accordingly. Abbreviation: (*n*) = (number of subjects), * = data of subethnic in the study were summarized into ethnics, nd = not determined in the respective study, ^ = study done on Singaporean populations.

4 CONCLUSION

Though the *CYP2C19* gene polymorphisms are not relatively new in the area of pharmacogenetics research, yet there is still less data on its study compared to the study of the isoform, *CYP2C9* gene. The lack of interest to disclose more on *CYP2C19* gene could be due to lower number of functional enzymes coded by the

gene than *CYP2C9*'s. Nevertheless, it cannot be concluded that *CYP2C19* gene has less importances and benefits in pharmacogenetics studies because both genes have a distinctive nature of metabolized drugs which will contribute to different effects in clinical implications. In fact, both genes have their own uniqueness and highly polymorphic attribution among various ethnic groups in the world [10,30]. Therefore, they supposedly need to be considered differently.

In SEA countries especially Malaysia, the study on *CYP2C9* and *CYP2C19* SNPs are still favourably wide to be scrutinized. Based on the available peer-reviewed studies, it is still difficult to conclude any firm inference on how Malaysian ethnic groups are responding to drugs that in relation to *CYP2C9* and *CYP2C19* polymorphisms. In fact, the SNP frequency demonstrated in some studies might not represent the prevalence of respective polymorphism in real populations due to small sample number investigated. Thus, this can become an opportunity and a strong reason for researchers to delve into deeper details on the genes and other SNPs of CYP. While environmental factors may also influence, the analysis of gene polymorphisms often provide the first hint on the drug disposition of individuals or among ethnic populations. Besides, an increasing number of cases describing adverse events to the drug administered emphasize the benefits of genotyping and its study prior to medication prescriptions [31]. The insufficient information could create challenges in order to apply pharmacogenetics tests in health premise.

Ideally, studies of CYP SNPs should be able to close the bridge between geneticist and clinical practitioner in providing better service of medical treatment. The collaboration between the clinicians and geneticists in pharmacogenetics field would be very fruitful in order to facilitate future generation who has safer and more effective drug dosing information. In fact, some of the information has already been translated in the current health premises. Therefore, the successful study of *CYP2C9* and *CYP2C19* SNPs should also be able to contribute in some aspects of drug regulations and dosages in Malaysia. With the implementation of the pharmacogenomics in public health settings, it will help to enhance drug treatment and assist the best dosage strategies among patients of different ethnic groups while wisely saving the government's funding on drugs expenses.

CONFLICTS OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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REFERENCES

[1] Ishikawa T, Tsuji A, Inui K, Sai Y, Anzai N, et al. The genetic polymorphism of drug transporters: functional analysis approaches. *Pharmacogenomics*. 2004; 5(1):pp.67-99.

[2] De Montellano O. *Cytochrome P450: Structure, Mechanism and Biochemistry*. New York; Springer, 2005.

[3] Ingelman-Sundberg M, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther*. 2007; 116:pp.496-526.

[4] Wolf CR, Smith G. Pharmacogenetics. *Br Med Bull*. 1999; 55(2):pp.366-386.

[5] Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. *Curr Drug Metab*. 2002; 3:pp.561-597.

[6] Demorais SM, Schweikl H, Blaisdell J, Goldstein JA. Gene structure and upstream regulatory regions of human *CYP2C9* and *CYP2C18*. *Biochem Biophys Res Commun*. 1993; 194:pp.194-201.

[7] Yang X, Zhang B, Molony C, Chudin E, Hao K, et al. Systematic genetic and genomic analysis of cytochrome P450 enzyme activities in human liver. *Genome Res*. 2010; 20:pp.1020-1036.

[8] Goldstein JA, de Morais SM. Biochemistry and molecular biology of the human CYP2C family. *Pharmacogenetics*. 1994; 4(6):pp.285-299.

[9] Romkes M, Faletto MB, Blaisdell JA, Goldstein J. *Cloning and Expression of Complementary DNAs for Multiple Members of the Human Cytochrome P450IIC Subfamily*. 1991.

[10] Daly AK. Pharmacogenetics of the major polymorphic metabolizing enzymes. *Fundam Clin Pharmacol*. 2003; 17:pp.27-41.

[11] Gerbal-Chaloin S, Daujat M, Pascussi JM, Pichard-Garcia L, Vilarem MJ, et al. Transcriptional regulation of *CYP2C9* gene. Role of glucocorticoid receptor and constitutive androstane receptor. *J Biol Chem*. 2002; 277:pp.209-217.

[12] Miners JO, Birkett DJ. Cytochrome P4502C9: An enzyme of major importance in human drug metabolism. *Br J Clin Pharmacol*. 1998; 45(6):pp.525-538.

[13] Lim JSL, Chen XA, Singh O, Yap YS, Ng RCH, et al. Impact of *CYP2D6*, *CYP3A5*, *CYP2C9* and *CYP2C19*

polymorphisms on tamoxifen pharmacokinetics in Asian breast cancer patients. *Br J Clin Pharmacol*. 2011; 71(5):pp.737-750.

[14] Zainuddin Z, Teh LK, Suhaimi AWM, Ismail R. Malaysian Indians are genetically similar to Caucasians : *CYP2C9* polymorphism. *J Clin Pharm Ther*. 2006; 31:pp.187-191.

[15] Seng KC, Gin GG, Sangkar JV, Phipps ME. Frequency of cytochrome P450 2C9 (*CYP2C9*) alleles in three ethnic groups in Malaysia. *Asian Pacific J Mol Biol Biotechnol*. 2003; 11(2):pp.83-91.

[16] Yang JQ, Morin S, Verstuyft C, Fan LA, Zhang Y, et al. Frequency of cytochrome P450 2C9 allelic variants in the Chinese and French populations. *Fundam Clin Pharmacol*. 2003; 17:pp.373-376.

[17] Yoon Y-R, Shon J-H, Kim M-K, Lim Y-C, Lee H-R, et al. Frequency of cytochrome P450 2C9 mutant alleles in a Korean population. *Br J Clin Pharmacol*. 2001; 51:pp.277-280.

[18] Miyuki K, Ichiro I, Kohsuke M, Akinori U, Shun H. Genetic polymorphisms of cytochrome P450s, *CYP2C19* and *CYP2C9* in a Japanese population. *Ther Drug Monit*. 1998; 20(3):pp.243-247.

[19] Rosdi R, Mohd Yusoff N, Ismail R, Choon T, Saleem M, et al. High allele frequency of *CYP2C9*3* (rs1057910) in a Negrito's subtribe population in Malaysia; Aboriginal people of Jahai. *Ann Hum Biol*. 2015.

[20] Imai J, Ieiri I, Mamiya K, Miyahara S, Furuumi H, et al. Polymorphism of the cytochrome P450 (CYP) 2C9 gene in Japanese epileptic patients : genetic analysis of the *CYP2C9* locus. *Pharmacogenetics*. 2000; 10:pp.85-89.

[21] Saab YB, Langaee T. Genetic polymorphisms of *CYP2C9*: Comparison of prevalence in the Lebanese population with other populations. *Pharmacol Pharm*. 2011; 2:pp.88-93.

[22] Dickmann LJ, Rettie AE, Kneller MB, Kim RB, Wood AJJ, et al. Identification and functional characterization of a new *CYP2C9* variant (*CYP2C9*5*) expressed among African Americans. *Mol Pharmacol*. 2001; 60(2):pp.382-387.

[23] Xie H-G, Prasad HC, Kim RB, Stein CM. *CYP2C9* allelic variants : ethnic distribution and functional significance. *Adv Drug Deliv Rev*. 2002; 54:pp.1257-1270.

[24] Rendic S, Di Carlo F. Human cytochrome P450 enzymes: a status report summarizng their actions, substrates, inducers, and inhibitors. *Drug Metab Rev*. 1997; 29:pp.413-580.

[25] Desta Z, Zhao X, Shin J-G, Flockhart DA. Clinical significance of the Cytochrome P450 2C19 genetic polymorphism. *Clin Pharmacokinet*. 2002; 41(12):pp.913-958.

[26] Ellis KJ, Stouffer GA, McLeod HL, Lee CR. Clopidogrel pharmacogenomics and risk of inadequate platelet inhibition: US FDA recommendations. *Pharmacogenomics*. 2009; 10(11):pp.1799-1817.

[27] Sim SC, Risinger C, Dahl M-L, Aklillu E, Christensen M, et al. A common novel *CYP2C19* gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. *Clin Pharmacol Ther*. 2006; 79(1):pp.103-113.

[28] Hu L-M, Dai D-P, Hu G-X, Yang J-F, Xu R, et al. Genetic polymorphisms and novel allelic variants of *CYP2C19* in the Chinese Han population. *Pharmacogenomics*. 2012; 13(14):pp.1571-1581.

[29] Mejin M, Tiong WN, Lai LYH, Tiong LL, Bujang AM, et al. *CYP2C19* genotypes and their impact on clopidogrel responsiveness in percutaneous coronary intervention. *Int J Clin Pharm*. 2013; 35(4):pp.621-628.

[30] Sistonen J, Fuselli S, Palo JU, Chauhan N, Padh H, et al. Pharmacogenetic variation at *CYP2C9*, *CYP2C19*, and *CYP2D6* at global and microgeographic scales. *Pharmacogenet Genomics*. 2009; 19(2):pp.170-179.

[31] Hitchen L. *Adverse Drug Reactions Result in 250,000 UK Admissions a Year*. Vol 332. 2006.