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Original Article

Single nucleotide polymorphisms on *CYP2C9* gene among Filipinos and its association with post-operative pain relief via COX-2 inhibitors

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Abstract: *CYP2C9* gene encodes an enzyme involved in the metabolism of a wide variety of drugs which include celecoxib. This study investigated the frequencies of the alleles and genotypes of *CYP2C9*1, CYP2C9*2,* and *CYP2C9*3* among Filipinos who underwent surgery, and to determine the association of *CYP2C9* polymorphisms with post-operative pain relief via COX-2 inhibitors. Response to celecoxib was determined using the numerical rating scale (0-10) on the 24th and 48th hour of surgery. The *CYP2C9* alleles were detected by real-time PCR. For *CYP2C9*1* and *CYP2C9*3*, the allele frequencies among Filipinos were 99% and 1% respectively, which is similar with other East Asians. *CYP2C9*2* alleles were not detected. The frequencies of *CYP2C9*1/*1* and *CYP2C9*1/*3* genotypes were 98% and 2% respectively. At 24 hours post-surgery, the average pain score was 2.57 ± 1.03, while on 48 hours post-surgery, the average pain score was 0.67 ± 0.61 among those who have the wild-type *CYP2C9*1* allele. The average pain score on the 24th and 48th hour post-operatively was observed to be 2.5 ± 0.71 and 0.5 ± 0.71 respectively among two patients classified as intermediate metabolizer carrying the *CYP2C9*1/*3* genotype. Low frequencies of *CYP2C9* polymorphisms were observed in the present study, this pattern was similar with other Asians except Indians, and considerably lower than Caucasians. Our results suggest that *CYP2C9* genotyping is not routinely needed for Filipinos but must be considered among mixed races. Consequently, a more personalized therapeutic strategy was derived from these data, resulting in good clinical outcomes and less adverse drug effects.

Keywords: Celecoxib, COX-2, *CYP2C9*1*, *CYP2C9*2*, *CYP2C9*3*, polymorphism, post-operative pain

Introduction

The cytochrome P450 2C9 (*CYP2C9*) is one of the enzymes responsible for the metabolism of a wide range of drugs such as anticoagulants, hypoglycemic agents, non-steroidal anti-inflammatory drugs (NSAIDs) and selective COX-2 inhibitors [1-4]. Polymorphisms in the *CYP2C9* gene have been associated with decreased enzyme activity and alteration of celecoxib pharmacokinetic parameters. Particularly, individuals with low enzyme activity (e.g. slow metabolizers) have a high propensity for adverse drug reactions [5].

CYP2C9 gene is located at chromosome 10q-23.33 which shows genetic polymorphisms. To date, more than 60 allelic variants of the *CYP-2C9* gene have been described [4]. *CYP2C9*1* is the wild-type allele and is associated with normal enzyme activity and normal metabolism of drugs. The two most common variants are *CYP2C9*2* and *CYP2C9*3*. The *CYP2C9*2* allele is the result of a 430C>T transition in exon 3 leading to an Arg-to-Cys substitution at amino acid position 144 of the *CYP2C9* molecule. On the other hand, *CYP2C9*3* is the result of a 1075A>C transversion in exon 7 causing an Ile-to-Leu substitution at amino acid position 359. Studies have shown that both alleles are associated with significantly reduced enzyme activity [6-8]. In addition, carriers of the *CYP2C9*3* variant are at risk for compli-

Table 1. Patient characteristics and type of surgery performed

Characteristics	Frequency n (%)
Sex	
Male	32 (32)
Female	67 (68)
Age	Mean 44
Surgery performed	
Thyroidectomy	56 (57)
Functional endoscopic sinus surgery	22 (22)
Tympanoplasty/mastoidectomy	9 (9)
Tonsillectomy	7 (7)
Excision biopsy	5 (5)

cations such as bleeding following use of warfarin. The frequencies of these two variants vary between different ethnic populations. For *CYP2C9*2,* the allele frequency among Caucasians ranges from 10-20%, whereas *CYP2C9*2* has not been detected among East Asian populations such as Chinese, Japanese and Koreans. For *CYP2C9*3,* the allele frequency among East Asians varies from 1-6% [1, 9].

Selective COX-2 inhibitor is a type of NSAID that has been utilized in post-operative pain management. Previous studies showed that COX-2 has some advantage over traditional or nonselective NSAID especially in certain group of patients undergoing tonsillectomy, eye and neurosurgical procedures, and other types of surgeries which contraindicate the use of traditional NSAID. Development of COX-2 and other pain relievers with less post-operative side effects made comeback investigations to effectively alleviate pain and suffering of post-operative patients and promote speedy recovery from surgery [10-12]. However, COX-2 administration despite its popularity, still requires cautious monitoring to prevent peri-operative adverse effects like traditional NSAID leading to renal injury, stomach ulcers and bleeding [13].

The distribution of *CYP2C9* gene polymorphisms have been extensively studied in many populations. However, data among Filipinos are lacking. Here, we determined the allelic and genotype frequencies of *CYP2C9*1*, *CYP2C9*2* and *CYP2C9*3* among Filipinos and compared with other ethnic populations. In addition, we investigated the association of *CYP2C9* polymorphisms with post-operative pain relief via COX-2 inhibitors. The characterization of *CYP2C9* polymorphisms among various ethnicity could contribute to the optimization of a wide range of drugs which include celecoxib.

Materials and methods

Study participants

A total of 99 unrelated patients were enrolled in this prospective observational study covering the period of December 2017 to October 2019. There were 32 (32%) males and 67 (68%) females. The study included patients 21 to 60 years old, with American Society of Anesthesiologists (ASA) classification 1 and 2, who underwent ENT procedures such as thyroidectomy, functional endoscopic sinus surgery, tympanoplasty, mastoidectomy, tonsillectomy and excision biopsy (**Table 1**). This population was chosen because these patients were already on full diet following surgery, thus they can be given oral analgesics such as celecoxib. Patients were excluded if any of the following are present: history of COX-2 inhibitor allergy; those who took COX2 inhibitors or any analgesics in the pre-operative period; patients with history of gastrointestinal toxicity to NSAIDs; patients with creatinine of less than 30 ml/minute; pregnant; and patients with ischemic heart disease.

All patients enrolled for this study were Filipinos, ethnically and primarily Malay, Malay-Chinese, Malay-Polynesian, and those 4th generation Filipino American or Filipino-European descent. All patients signed written informed consent prior to their enrolment. This study was approved by the Institutional Ethics Review Committee of St. Luke's Medical Center.

Genomic DNA extraction and CYP2C9 genotyping by real-time PCR

Approximately 4 mL of blood was drawn from each patient in EDTA anti-coagulated tube. Genomic DNA was isolated and purified using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) according to manufacturer's instructions. The DNA concentration and purity were analyzed using Nanodrop 1000 spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA). Genotyping of *CYP2C9*2* and *CYP-*

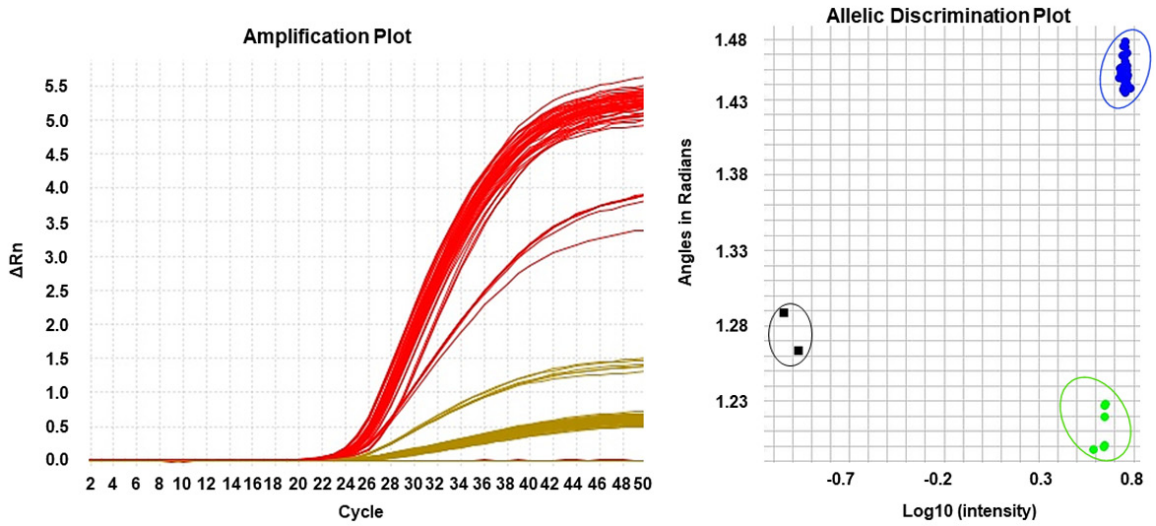

Figure 1. Representative amplification plot for real-time PCR using the 5' nuclease assay. Allelic discrimination plot showing a cluster of samples categories as AA genotype, homozygous wild-type (blue); AC genotype, heterozygous (green); and no template controls (black).

*2C9*3* variants was carried out using ABI™ 7500 Fast Real-Time PCR System (Applied Biosystems, California, USA) based on 5' nuclease assay (**Figure 1**). The two variants were genotyped in separate SNP Assays: SNP ID rs1799853 for *CYP2C9*2* and SNP ID rs1057910 for *CYP2C9*3* but utilized the same run method (hold at 95°C for 10 min followed by 50 cycles of 92°C for 15 min and 60°C for 1 min and 30 sec). Negative and no template controls were included for every run to ensure the quality of genotyping results. Allelic discrimination analysis of *CYP2C9*2* and *CYP2C9*3* variations was performed using SDS 2.3 software (Applied Biosystems, California, USA) (**Figure 1**).

Post-operative pain management

On the day of every patient's surgery, standard ASA monitoring was performed including non-invasive blood pressure monitoring, pulse oximetry, capnography, and electrocardiogram. The patients were given 40 mg intravenous (IV) dose of parecoxib intraoperatively. Twelve hours after the IV dose, post-operative care was initiated by administration of first 200 mg oral dose of celecoxib. Likewise, the same oral dose was given within 24 to 48 hours post-operative period. Follow up was done to check the patient's response to celecoxib and this was accomplished using the numerical pain score on the 24th and 48th hour post-operative period. Tramadol was chosen as rescue medication for standardization, it was administered in 50 mg IV dose every 8 hours as needed for pain score of greater than 4 (scale of 0 to 10) despite intake of celecoxib (**Table 2**).

Statistical analysis

Data were analyzed using the SPSS software and GraphPad QuickCalcs for categorical data (GraphPad Software, California, USA). Hardy-Weinberg Equilibrium was analyzed by the chi-square test. The genotype distribution and allele frequencies were estimated using 95% confidence interval for every observed proportion. Fisher's exact test was used to compare allele frequencies of *CYP2C9*2* and *CYP2C9*3* polymorphism obtained from this study to other population. A *P* value of less than .05 was considered statistically significant.

Results

*Allele and genotype frequencies of CYP2C9*1/*2/*3 single nucleotide polymorphisms among Filipinos*

The frequency of *CYP2C9*1/*2/*3* alleles were 99%, 0% and 1% respectively. Ninety-eight percent (97/99) of the patients were genotyped as *CYP2C9*1/CYP2C9*1* and 2% (2/99) as *CYP2C9*1/CYP2C9*3* (**Table 3**). The observed genotype frequency distribution of *CYP2-*

Table 2. Numerical rating scale for pain assessment

Score	Interpretation	Classification of patients according to drug response	Class definition
0	No pain	Responder	NRS of 0-3 after being given 1 dose of celecoxib
1-3	Mild pain	Responder	NRS of 0-3 after being given 1 dose of celecoxib
4-6	Moderate pain	Intermediate	NRS of 4-6 after being given more than 1 dose of celecoxib
7-10	Severe pain	Non-responder	NRS of 7-10 or those who have been given celecoxib but still needed rescue medications

NRS = numerical rating scale.

Table 3. *CYP2C9* genotype and allele frequency

Genotype distribution (*n* = 99 patients)		
Genotype	Frequency; *n* (%)	95% CI
*CYP2C9*1/CYP2C9*1*	97 (98)	92-100
*CYP2C9*1/CYP2C9*2*	0	0-4
*CYP2C9*1/CYP2C9*3*	2 (2)	0-8
*CYP2C9*2/CYP2C9*2*	0	0-4
*CYP2C9*2/CYP2C9*3*	0	0-4
Allele frequency (*n* = 198 alleles)		
Allele	Frequency; *n* (%)	95% CI
*CYP2C9*1*	196 (99)	96-100
*CYP2C9*2*	0	0-2
*CYP2C9*3*	2 (1)	0-4

Table 4. Frequency of *CYP2C9*2* and *CYP2C9*3* variants

*CYP2C9*2* genotype	n = 99	Prevalence (%)	95% CI
CC	99	100	95-100
CT	0	0	0-4
TT	0	0	0-4
Allele	Number of alleles	Frequency	95% CI
C	198	100	98-100
T	0	0	0-2
*CYP2C9*3* genotype			
AA	97	98	92-98
AC	2	2	0-8
CC	0	0	0-4
Allele	Number of alleles	Frequency	95% CI
A	196	99	96-100
C	2	1	0-4

*C9*3* did not show a deviation from the Hardy-Weinberg equilibrium.

None of the patients were found to be heterozygous (CT) or homozygous (TT) for *CYP2C9*2* alleles. On the other hand, *CYP2C9*3* genotyping showed prevalence of 98% (97/99) for the wild-type (AA) and 2% for the heterozygous (AC). No homozygous variant (CC) was identified in this study (**Table 4**).

Predicted phenotype and mean pain scores at 24 and 48-hours post-surgery

Based on the *CYP2C9* genotypes, patients predicted metabolizer phenotypes were used to assess and monitor the patient response to celecoxib. Homozygous wild-type was predicted to be extensive metabolizer, heterozygous variants were classified as intermediate metabolizer, while compound heterozygous and homozygous variants were poor metabolizer. In this study, the genotype-derived poor metabolizer phenotype was absent in the study population, whereas 98% (97/99) of the patients was predicted to be extensive metabolizer and 2% (2/99) to be intermediate metabolizers. At 24 hours post-surgery, the average pain score was 2.57 ± 1.03, while on 48 hours post-surgery, the average pain score was 0.67 ± 0.61 among those who have the wild-type *CYP2C9*1* allele. The average pain score on the 24th and 48th hour post-operatively was observed to be 2.5 ± 0.71 and 0.5 ± 0.71 respectively among two patients classified as intermediate metabolizer carrying the *CYP2C9*1/*3* genotype (**Table 5**).

*Allele frequencies of CYP2D6*2/*3 reported from various ethnic populations*

Table 6 shows the *CYP2C9*2* and *CYP2C9*3* allele frequencies among various populations. No significant differences were found between Filipinos and other Asians, except for North Indian population. The allele frequencies of *CYP2C9*2* and *CYP2C9*3* were significantly different (*P* = <.001) between Filipinos and Caucasian populations.

Table 5. Predicted phenotype and mean pain scores at 24 and 48-hours post-surgery

Genotype	Predicted phenotype	n = 99	Pain score (24 hours)	Pain score (48 hours)
Homozygous wild-type	Extensive metabolizer	97	2.57 ± 1.03	0.67 ± 0.61
*CYP2C9*1/CYP2C9*1*				
Heterozygous	Intermediate metabolizer	-	-	-
*CYP2C9*1/CYP2C9*2*		2	2.5 ± 0.71	0.5 ± 0.71
*CYP2C9*1/CYP2C9*3*				
Compound heterozygous	Poor metabolizer	-	-	-
*CYP2C9*2/CYP2C9*3*				
Homozygous variant	Poor metabolizer	-	-	-
*CYP2C9*2/CYP2C9*2*				
*CYP2C9*3/CYP2C9*3*				

Table 6. Comparison of *CYP2C9*2* and *CYP2C9*3* allele frequencies from various ethnic populations

Population	n	Number of alleles	*CYP2C9*2* frequency (*P* value)	*CYP2C9*3* frequency (*P* value)	Reference
Asian					
Filipino	99	198	0	1.0	Present study
Indian	89	178	4.5 (.0023)	10.1 (<.001)	[9]
Malay	183	366	1.0 (NS)	3.0 (NS)	[18]
Japanese	140	280	0 (NS)	1.8 (NS)	[20]
Korean	574	1148	0 (NS)	1.1 (NS)	[21]
Chinese	394	788	0.1 (NS)	3.6 (NS)	[22]
African					
Ethiopian	150	300	4.3 (.0023)	2.3 (NS)	[19]
Caucasian					
Romanian	332	664	11.3 (<.001)	9.3 (<.001)	[8]
Italian	157	314	11.0 (<.001)	9.0 (<.001)	[19]
French	151	302	15.0 (<.001)	8.0 (<.001)	[22]
British	100	200	12.5 (<.001)	8.5 (<.001)	[25]
American	100	200	8.0 (<.001)	6.0 (.01)	[26]
Swedish	430	860	10.7 (<.001)	7.4 (<.001)	[27]

P value was calculated using Fisher's exact test; NS = not significant.

Discussion

The frequency of *CYP2C9*1*, *CYP2C9*2* and *CYP2C9*3* have been reported in various ethnic populations worldwide [14-17]. The frequency of the wild-type allele *CYP2C9*1* and the common *CYP2C9*3* variant among Han Chinese were 94.48% and 2.94% respectively [5]. The frequency of the wild-type allele among Koreans was reported to be 0.934 [1]. In another study, the frequency of *CYP2C9*3* among Malays was 3% [18]. In contrast, the allele frequencies of *CYP2C9*1* (80%), *CYP2C9*2* (11%) and *CYP2C9*3* (9%) among Italians were similar with other Caucasian populations [19]. The results of the present study showed a frequency of 99% for *CYP2C9*1* and 1% for *CYP2C9*3* among Filipinos. Our findings are comparable to the frequencies of wild-type *CYP2C9*1* and *CYP2C9*3* variant allele among other East Asian populations. In this study, no *CYP2C9*2* variant was detected. This finding agreed with previous studies among East Asian countries like Japan, China, Korea, and Malaysia; suggestive that *CYP2C9*2* is rare or almost absent in this region [20-22]. Meanwhile, 2% of the patients were predicted as intermediate metabolizers for acquiring heterozygous *CYP2C9*3;* this variant has been reported to have reduced enzymatic activity. To the best of our knowledge, this is the first report of *CYP2C9* allele frequency

among Filipinos, which was also primarily used to assess the predicted metabolizer phenotypes of post-operative patients taking COX-2 inhibitors.

Patients with *CYP2C9*1/CYP2C9*3* genotype have responded well to celecoxib with the 24-hour mean pain score of 2.5 ± 0.71 and 48-hour mean pain score of 0.5 ± 0.71, even lower than those with homozygous *CYP2C9* 1.* However, considerations in the treatment strategies should be made since they were predicted as intermediate metabolizers compared to those participants which can rapidly eliminate the drug after delivery of therapeutic effect. Fortunately, celecoxib and other COX-2 inhibitors have a broad therapeutic window which may be favorable for these patients against unwanted adverse drug reactions. In 2016, Kim and colleagues reported that the plasma concentration of celecoxib and its final metabolite, celecoxib carboxylic acid was determined to correlate the effects of *CYP2C9* polymorphisms in drug clearance. This provided further information on how each phenotypic group differs in clearing celecoxib once it has delivered its therapeutic pain relief [23]. However, this study cannot confirm previous findings that the plasma concentration of celecoxib is correlated to the effects of *CYP2C9* polymorphisms. This serves as a limitation of this study.

The *CYP2C9* polymorphisms are relevant in terms of predicting the efficacy and adverse effects of NSAIDS, hypoglycemic agents and anticoagulants belonging to the class of vitamin K epoxide reductase inhibitors. Among the patients enrolled, there was no reported side effect encountered secondary to COX-2 inhibitor throughout the study period.

A similar study evaluated the relationship between polymorphisms in *CYP2C9* and the pharmacokinetics of celecoxib. The study demonstrated that individuals carrying *CYP2C9*1/CYP2C9*3* and *CYP2C9*3/CYP2C9*3* had lower clearance than those with the wild-type allele *CYP2C9*1/CYP2C9*1*. In addition, the half-life was noted to be 2.7-fold higher in patients with *CYP2C9*3/CYP2C9*3* than in those with the wild-type but not in those with *CYP2C9*1/CYP2C9*3* [24]. The findings of this study suggest that those who carry the *CYP2C9*3/CYP2C9*3* have poor metabolism of celecoxib thus, the dose of celecoxib be decreased in *CYP2C9*3* carriers.

Moreover, clinical case reports have associated genotypes expressing the *CYP2C9*2* and *CYP2C9*3* alleles with significant reductions in both metabolism and daily dose requirements of selected *CYP2C9* substrates. Individuals expressing these variant genotypes appear to be significantly more susceptible to adverse effects with the narrow therapeutic index agent warfarin and phenytoin, particularly during the initiation of therapy [6].

Genotyping of *CYP2C9* is expected to have a role in predicting drug clearance and implementing individualized pharmacotherapy. Prospective clinical studies with large samples are needed to establish gene-dose and gene-effect relationships for *CYP2C9* [28, 29]. Thus, future pharmacogenetic studies may be done to investigate other variants that may significantly influence celecoxib dosing among Filipinos.

The outcome of this study suggests that routine *CYP2C9* genotyping need not be performed among Filipinos but must be considered among mixed race patients most especially those with Caucasian lineage. This is to ensure that every patient will be treated with personalized care and prevent the occurrence of unnecessary adverse drug reactions.

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Disclosure of conflict of interest

None.

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