

# Prevalence of *CYP2C19*, *CYP3A4* and *FMO3* genetic polymorphisms in healthy northeastern Thai volunteers

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Received 13 Aug 2019

Accepted 23 May 2020

**ABSTRACT:** Voriconazole is the first-line drug for invasive aspergillosis infection treatment. It is metabolized via cytochrome P450 2C19 (*CYP2C19*), cytochrome P450 3A4 (*CYP3A4*) and flavin-containing monooxygenase 3 (*FMO3*). Many studies revealed the correlation between genetic polymorphisms of these SNPs and voriconazole metabolism. Several mutations, however, have not been reported in Thai population. Therefore, this study investigated the prevalence of *CYP2C19*, *CYP3A4* and *FMO3* polymorphisms. Two hundred and forty-nine healthy northeastern Thai volunteers who were blood donors at Srinagarind Hospital blood bank were enrolled. *CYP2C19* (\*2, \*3, \*17), *CYP3A4* (\*22, rs4646437G>A) and *FMO3* (rs2266782G>A, rs2266780A>G) mutations were investigated. The allele frequencies were *CYP2C19*\*1 (0.72), \*2 (0.24), \*3 (0.03) and \*17 (0.02) in this study. They were significantly different from Caucasian and Japanese populations. Moreover, *CYP3A4* rs4646437 allele frequencies were 0.76 for “G” and 0.24 for “A” alleles. The mutation of *CYP3A4*\*22 was not found in this study. Wild type (G) and mutation (A) allele frequencies of *FMO3* rs2266782 were 0.86 and 0.14, respectively. Similarly, the allele frequencies of *FMO3* rs2266780 for “A” (wild type) and “G” (mutant) were 0.89 and 0.11, respectively. Furthermore, a strong linkage disequilibrium was found between *FMO3* rs2266782 and rs2266780 genes ( $D' = 0.955$ ,  $r^2 = 0.7021$ ). The information on the SNP frequencies of *CYP2C19*, *CYP3A4* and *FMO3* in Thais was found to be significantly different from other populations. The genotype prevalence may be the preliminary information for a further clinical study to investigate the association between these genotypes and voriconazole treatment outcomes.

**KEYWORDS:** *CYP2C19*, *CYP3A4*, *FMO3*, polymorphisms, voriconazole

## INTRODUCTION

Voriconazole is a triazole antifungal agent with high potency against severe fungal infections such as aspergillosis and resistant candidiasis. Voriconazole is metabolized mainly by *CYP2C19* and partly by *CYP3A4* and *FMO3* [1–3]. Several studies reported genotype polymorphisms of these metabolizing enzymes correlated with voriconazole concentrations and dosage regimens. Voriconazole trough levels in poor metabolizers (PM) of *CYP2C19* (*CYP2C19*\*2/\*2, *CYP2C19*\*2/\*3 and *CYP2C19*\*3/\*3) were significantly higher than those in the normal metabolizer (NM) group (*CYP2C19*\*1/\*1). Ultra-rapid metabolizer carriers (URM, *CYP2C19*\*17/\*17) had the lowest trough concentrations. Moreover, *CYP2C19*\*17 carriers needed higher voriconazole dosage regimens to achieve the therapeutic range than NM and had a higher incidence of treatment failure than the wild

type. In contrast, PM patients had to have lower voriconazole doses prescribed than NM to achieve the therapeutic range and had a higher rate of hepatotoxicity than NM [3–9].

Recently, forty-seven alleles of *CYP2C19* genotype were reported. Nevertheless, only *CYP2C19*\*2, *CYP2C19*\*3 and *CYP2C19*\*17 were the most common mutations in Asian populations [4, 6, 7, 9]. The *CYP2C19*\*2; rs4244285, 681G>A caused splicing defects leading to a decrease in enzyme activity. The *CYP2C19*\*3; rs4986893, 636G>A caused a premature stop codon resulting in non-enzyme activity. In contrast, *CYP2C19*\*17; rs12248560, -806C>T, -3402C>T created an increased transcription leading to high enzyme activity. Different phenotypes resulting from the mutations are divided into four groups. First, normal metabolizers have normal enzymatic activity and have the *CYP2C19*\*1/\*1 genotype. Second, *CYP2C19*\*1/\*2 or *CYP2C19*\*1/\*3 people are categorized into intermediate metabo-

lizers (IM). The poor metabolizer group is for individuals with *CYP2C19*\*2/\*2, *CYP2C19*\*2/\*3 and *CYP2C19*\*3/\*3. People with the *CYP2C19*\*17 alleles (*CYP2C19*\*1/\*17 or *CYP2C19*\*17/\*17) are classified as an ultra-rapid metabolizer. A previous Thai population study found the allele frequencies of *CYP2C19*\*1, *CYP2C19*\*2, *CYP2C19*\*3 and *CYP2C19*\*17 were 63, 27, 6 and 4%, respectively. The *CYP2C19*\*2 allele frequency was similar to that of other Asian populations such as Japanese (29%), Han-Chinese (37%) and Korean (21%), but was different from Caucasians. The frequency of the *CYP2C19*\*3 in Thais was lower (6%) than in Japanese and Korean populations (12%) while no *CYP2C19*\*3 allele was detected in Caucasians [10].

The mutation of *CYP3A4* rs4646437 occurs at the 671-202 intron site of chromosome 7. The base changed from G to A. The effect on *CYP3A4* enzyme activity, however, is unclear. Shao et al [8, 11] revealed that *CYP3A4* rs4646437 polymorphism was correlated with voriconazole trough concentration. The mutation of *CYP3A4* rs4646437 affected an increase of voriconazole concentration. Following HapMap, mutant allele (A) frequency of *CYP3A4* rs4646437 was 10–13% in Asians and Europeans, 25% in Hispanic and 60–90% in African American and African populations. No prevalence of this SNP, however, has been reported in Thais. *CYP3A4*\*22 was another mutation of the *CYP3A4* genotype that showed the correlation with voriconazole levels. This mutation leads to a decrease in *CYP3A4* enzymatic activity due to the reduction of protein expression. Thus, voriconazole levels tended to rise in *CYP3A4*\*22 carriers [5]. This allele mutation was found in 5–7% of the Caucasian population [12].

A previous *in vitro* study proposed that 25% of voriconazole was metabolized via *FMO3* [3]. There is no study, however, indicating a correlation between *FMO3* polymorphism and voriconazole exposure. The mutation of *FMO3* was found to affect human disease, metabolism and toxicity of other drugs. *FMO3* variant alleles decreased enzyme activity [13]. Common variants of the *FMO3* genotype were rs2266782 (E158K, 15167G>A, exon 4), rs2266780 (E308G, 21443A>G, exon 7) and rs1736557 (V257M, 18281G>A, exon 6) [13]. Following HapMap data, *FMO3* rs2266782 allele frequencies in Caucasian and Asian populations were approximately 42% and 20%, respectively. Moreover, *FMO3* rs2266780 allele frequencies in Caucasian, Asian and African populations were approximately 22%, 18% and 1%, respectively. Only 7.1% of *FMO3* rs1736557 was found in Caucasian,

14% in Asian and 2% in African populations [14]. A previous study reported that the mutation of *FMO3* rs1736557 presented a normal phenotype. It slightly reduced the enzyme activity in sulindac metabolism [13]. Another variant was *FMO3* rs909530 (N285N, C>T, Exon 5), of which allele frequency was found in approximately 38% in Asian, 28% in European population and 54% in African populations [14]. This mutant allele significantly decreased protein abundance [15].

In Thai population, the prevalence of *CYP2C19* has been studied [10]. *CYP3A4* and *FMO3* mutations have not been reported. This study aimed to investigate the prevalence of *CYP2C19*, *CYP3A4* and *FMO3* genetic polymorphisms related to voriconazole metabolic pathway in healthy northeast Thai volunteers. Therefore, the prevalence of these genes would be the initial information to investigate further the association between genetic polymorphisms and voriconazole treatment in Thai population. The prevalence of these genotypes may be useful for the physicians to consider the significance of this mutation effecting voriconazole treatment in the future.

## MATERIALS AND METHODS

### Subjects

Two-hundred and forty-nine of healthy northeastern Thai volunteers were enrolled in this study at the Central Blood Bank, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. The volunteers were enrolled following two inclusion criteria. First, their age was more 18 years. Second, they are the northeastern Thais that were tested back to three generations. This study was carried out based on the Declaration of Helsinki and the ICH Good Clinical Practice Guidelines approved by the Ethics Committee for Human Research, Khon Kaen University (HE601155).

### DNA extraction and genotyping

Three milliliters of blood were collected from each patient and then centrifuged to collect the buffy coat. The buffy coat was extracted by QIAamp® DNA Blood Mini Kits according to the manufacturer's instruction. The gDNA products were evaluated by using the NanoDrop. The purity of DNA was accepted in the range of 260/280 at 1.8–2.0. DNA concentration of the sample was more than 20 ng/μl. The mutations were detected in all seven SNPs (*CYP2C19*\*2, *CYP2C19*\*3, *CYP2C19*\*17, *CYP3A4* rs4646437, *CYP3A4*\*22, *FMO3* rs2266782

and *FMO3* rs2266780). The genotyping was performed following TaqMan allelic discrimination assay by using the Light-Cycler 480 technology (Roche Diagnostics, Meylan, France) according to the manufacturer’s instruction.

**Statistical analysis**

All frequencies were analyzed with the Hardy-Weinberg equilibrium on the Online Encyclopedia for Genetic Epidemiology studies web tool (OEGE) [16]. Pearson’s Chi-square test or Fisher’s exact test by SPSS was conducted to compare the differences in the prevalence of allele frequencies of the Thai population and other ethnicities. Linkage disequilibrium was calculated by the Cubic Exact Solution (CubeX) [17].

**RESULTS**

Results of *CYP2C19* polymorphisms of two hundred and forty-nine northeastern Thai volunteers were summarized in Table 1 and Table 2. The allele frequencies were *CYP2C19*\*1 (0.72), \*2 (0.24), \*3 (0.03) and \*17 (0.02) in this study. There were 51.4% (*n* = 128) identified as *CYP2C19*\*1/\*1 (NM). Ninety-four volunteers (37.8%) were identified as IM (*CYP2C19*\*1/\*2, \*1/\*3). PM (*CYP2C19*\*2/\*2, \*2/\*3) was found in 7.6% (*n* = 19). *CYP2C19*\*1/\*17 was 2.4% (*n* = 6) and was categorized as URM. Moreover, *CYP2C19*\*2/\*17 was found in one volunteer (0.8%). The allele frequencies of *CYP2C19* in this study were significantly different from those of several ethnicities except for previous northeastern Thai studied and Chinese (Table 3).

One hundred and forty-seven volunteers (59%) in this study were presented as the wild type allele (GG) of *CYP3A4* rs4646437 while eighty six (34.6%) of volunteers carried the heterozygous mutant (GA) of *CYP3A4* rs4646437. The homozygous mutant (AA) of *CYP3A4* rs4646437 was detected in sixteen volunteers (6.4%). The allele frequencies of “G” and “A” of *CYP3A4* rs4646437 were 76.3% (*n* = 380)

**Table 1** *CYP2C19* allele frequencies in healthy Thai volunteers.

<i>CYP2C19</i>	Number	Frequency
*1	356	0.71
*2	119	0.24
*3	15	0.03
*17	8	0.02
Total	498	1.00

**Table 2** *CYP2C19* genotype and phenotype frequencies in healthy northeastern Thai volunteers.

Predicted phenotype <sup>†</sup>	Genotype	No.	Frequency (%)	
			Genotype	Phenotype
NM	*1/*1	128	51.41	51.41
IM	*1/*2	82	32.93	37.75
	*1/*3	12	4.82	
PM	*2/*2	16	6.43	7.63
	*2/*3	3	1.20	
URM	*1/*17	6	2.41	2.41
N/A	*2/*17	2	0.80	0.80
Total		249	100	100

<sup>†</sup> NM, normal metabolizer; IM, intermediate metabolizer; PM, poor metabolizer; URM, ultra-rapid metabolizer; and N/A, unidentified.

and 23.7% (*n* = 118), respectively. The frequencies were significantly different from both Asians and Caucasians (Table 4) [11, 18, 19]. The *CYP3A4*\*22 mutant allele was not found in this study.

Genotype frequencies of *FMO3* rs2266782 in this study were GG 73.5% (*n* = 183), GA 25.3% (*n* = 64) and AA 1.2% (*n* = 2) (Table 5). The allele frequencies of “G” and “A” in this study were 86.4% (*n* = 430) and 13.6% (*n* = 68), respectively. Furthermore, these were significantly different from Caucasians, African-Americans, Hispanics and Asians except for Koreans [20–23]. For *FMO3* rs2266780 in this study, the genotype frequencies were 78.8% (*n* = 196) for wild type (AA), 20.6% (*n* = 52) for heterozygous mutant (AG) and 0.6% (*n* = 1) for homozygous mutant (GG) (Table 6). There were 89.2% (*n* = 444) for “A” allele and 10.8% (*n* = 54) for “G” allele. *FMO3* rs2266780 allele mutants were significantly different between Thais and Caucasians, African Americans and Asians. There was no significant difference between Thais and Hispanics [20–23]. All SNPs in this study were following the Hardy-Weinberg equilibrium (*p* > 0.05). Moreover, *FMO3* rs2266780 and rs2266782 showed strong linkage disequilibrium (*D'* = 0.955, *r*<sup>2</sup> = 0.7021).

**DISCUSSION**

Several previous studies reported the prevalence of *CYP2C19* polymorphisms. Tassaneeyakul et al [24] first reported the prevalence in the northeastern Thai population of *CYP2C19* in 2002. The result showed similar allele frequencies of *CYP2C19*\*2 and *CYP2C19*\*3 between Tassaneeyakul’s study and this study. This similarity was because the subjects of

**Table 3** *CYP2C19* allele frequencies from different ethnicities.

Ethnic group	n	<i>CYP2C19</i> allele				p-value	Ref.
		1*	2*	3*	17*		
Northeastern Thai	498	0.71	0.24	0.03	0.02		This study
Northeastern Thai	214	0.71	0.27	0.02	NA	0.247 <sup>a</sup>	Tassaneeyakul [24]
Thai	2102	0.64	0.28	0.06	0.02	0.003 <sup>a</sup>	Sukasem [10]
Japanese	530	0.58	0.28	0.13	0.01	< 0.001 <sup>a</sup>	Sugimoto [27]
Korean	200	0.65	0.25	0.08	0.02	0.032 <sup>a</sup>	Myrand [26]
Chinese	200	0.67	0.29	0.03	0.01	0.342	Myrand [26]
Caucasian	282	0.66	0.14	–	0.20	< 0.001 <sup>a</sup>	Myrand [26]
Ugandan	198	0.69	0.13	0.01	0.17	< 0.001 <sup>a</sup>	Miura [25]
Russian	1942	0.58	0.14	0.01	0.27	< 0.001 <sup>a</sup>	Sychev [28]

<sup>a</sup> The mean difference is significant at the 0.050 level; NA = not available.

**Table 4** *CYP3A4* rs4646437 genotype and allele frequencies from different ethnicities.

Ethnic group	n	<i>CYP3A4</i> (rs4646437) genotype (%)			Allele		p-value	Ref.
		GG	GA	AA	G	A		
Thai	249	147 (59.0)	86 (34.5)	16 (6.4)	0.76	0.24		This study
Chinese	158	122 (77.2)	35 (22.2)	1 (0.6)	0.88	0.12	< 0.001 <sup>a</sup>	He [11]
Japanese	172	136 (79.1)	32 (18.6)	4 (2.3)	0.88	0.12	< 0.001 <sup>a</sup>	Hapmap
Caucasian	73	61 (83.6)	12 (16.4)	0 (0.0)	0.92	0.08	< 0.001 <sup>a</sup>	Crettol [18]
Egyptian	50	16 (32.0)	24 (48.0)	10 (20.0)	0.56	0.44	< 0.001 <sup>a</sup>	Sharaki [19]

<sup>a</sup> The mean difference is significant at the 0.050 level.

**Table 5** *FMO3* rs2266782 genotype and allele frequencies from different ethnicities.

Ethnic group	n	<i>FMO3</i> (rs2266782, E158K) genotype (%)			Allele		p-value	Ref.
		GG	GA	AA	G	A		
Thai	249	183 (73.53)	64 (25.29)	2 (1.18)	0.86	0.14		This study
Han Chinese	220	133 (60.46)	73 (33.18)	14 (6.36)	0.77	0.23	< 0.001 <sup>a</sup>	Ren [23]
Korean	219	147 (67.12)	61 (27.86)	11 (5.02)	0.81	0.19	0.028 <sup>a</sup>	Park [22]
Japanese	172	108 (62.79)	52 (30.23)	12 (6.98)	0.78	0.22	0.001 <sup>a</sup>	Hapmap
Caucasian	439	153 (34.85)	211 (48.07)	75 (17.08)	0.59	0.41	< 0.001 <sup>a</sup>	Hao [21]
African-American	328	103 (31.40)	160 (48.78)	65 (19.82)	0.56	0.44	< 0.001 <sup>a</sup>	Hao [21]
Hispanic	85	36 (42.35)	38 (44.71)	11 (12.94)	0.65	0.35	< 0.001 <sup>a</sup>	Cashman [20]

<sup>a</sup> The mean difference is significant at the 0.050 level.

**Table 6** *FMO3* rs2266780 genotype and allele frequencies from different ethnicities.

Ethnic group	n	<i>FMO3</i> (rs2266780, E308G) genotype (%)			Allele		p-value	Ref.
		GG	GA	AA	G	A		
Thai	249	196 (78.82)	52 (20.59)	1 (0.59)	0.89	0.11		This study
Han Chinese	220	140 (63.64)	67 (30.45)	13 (5.91)	0.79	0.21	< 0.001 <sup>a</sup>	Ren [23]
Korean	219	149 (68.04)	60 (27.40)	10 (4.56)	0.82	0.18	0.001 <sup>a</sup>	Park [22]
Japanese	172	114 (66.28)	50 (29.07)	8 (4.65)	0.81	0.19	0.001 <sup>a</sup>	Hapmap
Caucasian	231	159 (68.83)	63 (27.27)	9 (3.90)	0.82	0.18	0.003 <sup>a</sup>	Hao [21]
African-American	328	305 (92.99)	22 (6.71)	1 (0.30)	0.96	0.04	< 0.001 <sup>a</sup>	Hao [21]
Hispanic	85	66 (77.65)	17 (20.00)	2 (2.35)	0.88	0.12	0.590	Cashman [20]

<sup>a</sup> The mean difference is significant at the 0.050 level.

both studies were from the same native area. However, the study of Tassaneeyakul et al [24] did not determine the allele frequency of *CYP2C19\*17*. The *CYP2C19* allele frequencies in this study were significantly different from Sukasem's study and other studies in Japanese, Caucasian, Ugandan and Russian populations [10, 25–28]. No difference in allele frequencies was found among other Asians such as Chinese and Korean [26]. Differences of *CYP2C19* allele frequencies among the Thai population may be due to the different regions of subject origins between this study and Sukasem's study [10]. In this study, volunteers were enrolled from the northeastern of Thailand while the origins of the volunteers of Sukasem's report were not described [10]. The *CYP2C19\*3* allele frequency of northeastern Thais was two-fold lower than that of Sukasem's study.

*CYP3A4* rs4646437 was another SNP that was published influencing voriconazole plasma concentrations in Chinese [8, 11]. In this study, the mutant allele (A) frequency of *CYP3A4* rs4646437 was different from other ethnicities. The Thai population had a higher allele frequency of "A" allele than either Asians or Caucasians (24%, 12% and 8%, respectively) [8]. Therefore, *CYP3A4* rs4646437 mutation might play an important role in voriconazole metabolism in Thai patients.

Many publications revealed the correlation between the mutations of the *FMO3* gene and the fish-odor syndrome and other drug responses [13]. The previous study reported that the mutation of the gene encoding *FMO3* enzyme might affect voriconazole metabolism and play a role of up to 20% [3]. In the Thai population, the *FMO3* allele frequency was not reported. Therefore, *FMO3* rs2266782 and rs2266780 that had been reported for the association was selected to be determined in Thais. In this overview, both SNPs frequencies were significantly different from Asians, Caucasians, African Americans and Hispanics. *FMO3* rs2266782 in Thais showed a lower frequency than in other ethnic populations. Yamazaki and Shimizu [14] revealed that the mutation of *FMO3* rs2266782 coincided with the mutation of *FMO3* rs2266780, causing more interruption of the enzyme function. Linkage disequilibrium (LD) was found between *FMO3* rs2266782 and rs2266780 in this study ( $D' = 0.955$ ,  $r^2 = 0.7021$ ). Likewise, the LD of these two SNPs was displayed in other Asian populations such as Chinese ( $D' = 0.977$ ,  $r^2 = 0.944$ ) and Korean ( $D' = 0.969$ ,  $r^2 = 0.897$ ) [29]. However, the linkage in Chinese was stronger than in Korean and this study, suggesting that the linkage was variable among the

populations. In contrast, there was no LD report of these SNPs in other ethnic groups.

In conclusion, the prevalence differences of *CYP2C19*, *CYP3A4* and *FMO3* polymorphisms of the Thai population from many ethnicities may lead to variations in the voriconazole dosage regimens, risk of toxicity and therapeutic outcomes. Therefore, we are investigating the association between *CYP2C19*, *CYP3A4* and *FMO3* polymorphisms and voriconazole concentration, clinical outcome and toxicity, respectively, in Thais.

**Acknowledgements:** The authors sincerely thank all staff at Central Blood Bank, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, for supporting this research. Miss Thikhumporn Areesinpitak was supported by the Research Fund for supporting lecturer to admit high potential students to study and research on his expert program year 2015, the grant of Graduate School, Khon Kaen University. This study was supported by Thailand Science Research and Innovation (TSRI) (RSA6180028). We would like to acknowledge James A. Will, Emeritus Professor, University of Wisconsin-Madison for editing the manuscript via Publication Clinic KKU, Thailand.

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