Distribution of *pfmdr1* polymorphisms in *Plasmodium falciparum* isolated from Southern Thailand

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**Abstract**

**Background:** Drug resistance in *Plasmodium falciparum* is a major problem in malaria control especially along the Thai-Myanmar and Thai-Cambodia borders. To date, a few molecular markers have been identified for anti-malarial resistance in *P. falciparum*, including the *P. falciparum* chloroquine resistance transporter (*pfcrt*) and the *P. falciparum* multidrug resistance 1 (*pfmdr1*). However no information is available regarding the distribution pattern of these gene polymorphisms in the parasites from the Thai-Malaysia border. This study was conducted to compare the distribution pattern of the *pfcrt* and *pfmdr1* polymorphisms in the parasites from the lower southern provinces, Thai-Malaysia border and the upper southern provinces, Thai-Myanmar border. In addition, *in vitro* sensitivities of anti-malarial drugs including chloroquine, mefloquine, quinine, and artesunate were determined.

**Methods:** In all, 492 *P. falciparum*-positive blood samples were collected from the lower southern provinces: Songkhla, Yala and Narathiwas. From the upper southern part of Thailand, Ranong and Chumphon, 66 samples were also collected. Polymorphisms of the *pfcrt* and the *pfmdr1* gene were determined using PCR techniques. *In vitro* sensitivities of anti-malarial drugs were determined using radioisotopic method.

**Results:** All parasites from both areas contained the *pfcrt* 76 T allele. The *pfmdr1* 86Y allele was significantly more common in the parasites isolated from the lower southern areas. In contrast, the *pfmdr1* 184F allele was predominant among the parasites from the upper southern areas especially Ranong. In addition, the parasites from Ranong contained higher copy numbers than the parasites from other provinces. All adapted parasite isolates exhibited CQ-resistant phenotype. Neither QN nor MQ resistance was detected in these isolates.

**Conclusion:** The parasites from Thai-Malaysia border exhibited different resistant patterns compared to other areas along the international border of Thailand. This information will be useful for anti-malarial drug policy in Thailand.

**Background**

Multidrug resistance in *Plasmodium falciparum* has been a major problem in malaria control along the international borders of Thailand especially, Thai-Myanmar and Thai-Cambodia border [1]. Artemisinin-based combination therapy (ACT), using a combination of artesunate (ART) and mefloquine (MQ), has been introduced for the treatment of uncomplicated falciparum malaria to address this problem [2]. In the past few years, emergence of artemisinin resistance in these areas is a matter of concern [3,4]. Prolonged parasite clearance has now been used as the indicator of artesiminisin resistance [4].

A few molecular markers have been identified for anti-malarial resistance in *P. falciparum*. The *P. falciparum* chloroquine resistance transporter (*pfcrt*) has been identified as the main determinant of chloroquine (CQ) resistance [5]. A point mutation on the *pfcrt* gene resulting in replacement of lysine by threonine in the PfCRT at codon 76 has been linked to CQ resistance in parasite isolates collected worldwide [6]. The *P. falciparum* multidrug resistance 1 (*pfmdr1*), a gene on chromosome 5 encoding a P-glycoprotein homologue 1 (*pgh1*) also contributes to CQ resistance [7-10]. Several studies have shown that single nucleotide polymorphisms and amplification of the...
The pfmdr1 gene is also associated with in vitro response and clinical efficacy of MQ, an arylaminoalcohol [11-14]. Evidence suggests that the pfmdr1 gene plays a role in the in vitro response to other quinolines such as quinine (QN) and lumefantrine (LF) and artemisinin derivatives [15-18].

To date, the distribution of the pfcr and pfmdr1 polymorphisms were only reported in the parasites collected from the Thai-Myanmar and Thai-Cambodia borders, but not the Thai-Malaysia border [10,13,14,17,18]. Since different patterns of pfcr and pfmdr1 polymorphisms in P. falciparum exhibit varied anti-malarial drug susceptibilities [10,17,18], knowing the distribution of these polymorphisms in these areas would be useful. In this study, the pfcr and pfmdr1 polymorphisms in P. falciparum isolated from the Thai-Malaysia border were determined compared with the parasites isolated from upper southern provinces, Thai-Myanmar border. In addition, the in vitro sensitivities of anti-malarial drugs including CQ, MQ, QN and ART were determined in recently adapted parasites from the Thai-Malaysia and Thai-Myanmar border. Each in vitro sensitivity experiment was carried out in triplicate. The IC50 of each isolate was the mean IC50 of at least three independent experiments.

**Genotypic characterization for pfcr and pfmdr1 genes**
Parasite DNA was extracted using the Chelex-resin method [22]. Five μl of DNA preparation was used for a 25 μl PCR reaction. PCR and allele-specific restriction analysis were performed for the detection of the pfcr mutations encoded amino acids at position 76 [23]. Mutations in the pfmdr1 gene were determined by the nested PCR and restriction endonuclease digestion method developed by Duraisingh et al. [15] for detection of the mutations at codons 86, 184, 1034, 1042 and 1246 [24]. K1, a laboratory strain containing the 86Y allele was used as a control for the detection of the N86Y mutation. For the positive control of the 184 F, 1034C, 1042D and 1246Y alleles, 7G8 strain was used. The results with a combined band pattern of undigested and digested fragments were considered mixed alleles. The pfmdr1 gene copy number was determined by TaqMan real-time PCR (ABI sequence detector 7000; Applied Biosystems) as developed by Price et al. [25]. The K1 and DD2 clone containing 1 and 4 pfmdr1 copies, respectively, was used as the reference DNA sample. The pfmdr1 and β-tubulin amplification reactions were run in duplicate. Relative copy number of the pfmdr1 gene was determined as previously described [25].

**Statistical analysis**
Data were analysed by STATA/MP, Version 12. Differences of the mean copy number of the pfmdr1 gene among the parasites from different areas were analysed by Independent t test and One-way ANOVA. Post hoc test (Scheffe) for multiple comparisons was used to test for differences among groups. Association between genotypes and P. falciparum from different areas was analysed by Chi square test. The level of significance was set at a p value of < 0.05.

**Results**

Characterization of the pfcr and pfmdr1 genes
Genotypic characterization of the parasite isolates from upper and lower southern Thailand is shown in Table 1 and Figure 1. All parasites from both areas contained the pfcr 76T allele. Of the 492 parasite isolates from lower southern Thailand, 474 (96.3%), 16 (3.3%), and two (0.4%) isolates contained the pfmdr1 86Y, 184F and 1034C mutations, respectively. The distribution of the pfmdr1 polymorphisms of the parasites isolated among three lower...
southern provinces, i.e. Yala, Narathiwas and Songkhla, was similar. The pfmdr1 86Y allele was significantly more common in the parasites isolated from lower southern areas than those isolated from upper southern areas (Chi square, \( p < 0.001 \)). In contrast, the pfmdr1 184F allele was more common in the parasites from upper southern areas (Chi square, \( p < 0.001 \)). In this area, the pfmdr1 184F allele was significantly more common in the parasites isolated from Ranong compared to those from Chumphon (Chi square, \( p < 0.001 \)). In contrast, the pfmdr1 86Y allele was significantly predominant in the parasites from Chumphon (Chi square, \( p < 0.001 \)). Parasites containing mixed alleles of the pfmdr1 gene were not detected in all samples.

Determination of the pfmdr1 gene copy number showed that the isolates from upper southern areas contained the pfmdr1 copy numbers with the mean of 2.3 (range 1 to 4) which was significantly higher than those found in the

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**Table 1** Distribution of the pfcr7 and pfmdr1 polymorphisms of the parasites isolated from upper and lower southern areas

| Area             | No. of isolates | pfcr 76T | Mean pfmdr1 copy number | pfmdr1 mutations |
|------------------|-----------------|----------|-------------------------|------------------|
|                  |                 |          | 86Y | 184F | 1034C | 1042D | 1246Y |
| Upper southern   | 66              | 66 (100%)| 2.3 ± 1.0*               | 24 (36.4%)**     | 42 (63.6%)** |
| Ranong           | 42              | 42 (100%)| 2.6 ± 0.8                | 6 (14.3%)        | 36 (85.7%)   |
| Chumphon         | 24              | 24 (100%)| 1.7 ± 0.9                | 18 (75.0%)       | 6 (25.0%)    |
| Lower southern   | 492             | 492 (100%)| 1.2 ± 0.4               | 474 (96.3%)      | 16 (3.3%)    |
| Yala             | 215             | 215 (100%)| 1.3 ± 0.5               | 204 (94.9%)      | 10 (4.7%)    |
| Narathiwas       | 234             | 234 (100%)| 1.2 ± 0.4               | 228 (97.4%)      | 5 (2.1%)     |
| Songkhla         | 43              | 43 (100%)| 1.2 ± 0.4               | 42 (97.7%)       | 1 (2.3%)     |

*Significant difference between parasites isolated from upper and lower southern area determined by Independent t test (\( p < 0.001 \)).

**Significant difference between parasites isolated upper and lower southern area determined by Chi square test (\( p < 0.001 \)).

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**Figure 1** Predominant pfmdr1 genotypes in different areas of Thailand. The present study locations including two provinces in the upper south, (1) Chumphon and (2) Ranong and three provinces in the lower south, (3) Songkhla, (4) Yala and (5) Narathiwas and previously reported areas including (6) Tak and (7) Kanchanaburi [17,18,31], (8) Chantaburi and (9) Trat [17,18,29].
parasite from lower southern areas (mean = 1.2, range 1 to 3). Significant differences of the \( pfmdr1 \) copy numbers were found among the parasites from different provinces (One-way ANOVA, \( p < 0.001 \)). Multiple comparison indicated that the parasites from Ranong contain more copy number than the parasites from Chumphon, Yala, Narathiwats and Songkhla (all \( p < 0.001 \)). The parasites from Chumphon also had more copy number than the parasites from lower southern areas, i.e. Yala, Narathiwats and Songkhla (\( p = 0.007 \), \( p = 0.004 \), and \( p = 0.012 \), respectively).

**In vitro** anti-malarial sensitivities against 15 *Plasmodium falciparum* isolates from Yala

Table 2 shows in vitro response of parasites isolated from Yala to four commonly used anti-malarial drugs. All isolates exhibited CQ-resistant phenotype [26]. Neither QN resistance (QN IC\( 50 \) of > 800 nM) [27] nor MQ resistance (MQ IC\( 50 \) of > 30 nM) [28] was detected in these isolates. All isolates contained the \( pfcrt \) 76T and a single copy of the \( pfmdr1 \) gene with the 86Y allele.

**Discussion**

Majority of *P. falciparum* isolates collected from three provinces along the Thai-Malaysian border, i.e. Yala, Narathiwats and Songkhla, contained the \( pfmdr1 \) 86Y allele (96.3%) with the mean copy number of 1.2. Malaria cases in the southernmost provinces have significantly increased since 2005, after political unrest in this area. Previously, in the southernmost provinces have significantly increased (96.3%) with the mean copy number of 1.2. Malaria cases in Thailand might be due to the response to a different drug pressure in the past. Since 1995, the combination of ART/MQ has been adopted by the Ministry of Public Health for the treatment of uncomplicated falciparum malaria in Thailand [1,32,33]. In the beginning, this combination was used only in the highly MQ-resistant areas, including the Thai-Myanmar area, Tak and the Thai-Cambodia area, Trat and Chantaburi. In some areas of the Thai-Myanmar border, including Ranong, ART has been added just a few years later. In addition, dosage of ART and MQ might vary among different areas. For example, in 2002, a single dose of 15 mg/kg of MQ was used in the non- or low MQ-resistant areas of this province, divided doses of 12 mg/kg ART were added. In contrast, in the high MQ-resistant areas such as Mae Sod, Tak province, a combination of 25 mg/kg of MQ and 12 mg/kg of ART was used. The combination of ART/MQ has been used in the malaria clinics of the Office of Disease Prevention and Control in these southernmost provinces since 2004. However, a few hospitals in the area might use other regimens such as a combination of QN/doxycycline. In addition, in Thailand, vivax malaria shares similar endemic areas with falciparum malaria. Thus, CQ, the first-line treatment for vivax malaria could cause a drug pressure and influence the distribution of the \( pfmdr1 \) polymorphisms, especially where vivax malaria was predominant.

The distribution of the \( pfmdr1 \) polymorphisms in each area along the international border of Thailand might be influenced by the parasites from neighbouring countries via human movement. Indeed, approximately half of malaria cases in Thailand have been foreign migrant workers [34]. A few studies of the parasites from the Thai-Cambodia border showed that most parasites collected either from Thailand or Cambodia shared a similar genotype, i.e., the \( pfmdr1 \) 184F allele [29,30]. A recent study showed a high level of genetic diversity in the parasites from the Thai-Myanmar and Thai-Cambodia border where cross-border migrations commonly occurred [35]. This study also identified the parasites with the same genotype in patients who were infected in Thailand and Myanmar [35]. In contrast, an identical haplotype was

**Table 2** In vitro anti-malarial sensitivities in 15 *P. falciparum* isolates from Yala

| Drug      | IC\( 50 \) (nM) | IC\( 30 \) (nM) | IC\( 20 \) (nM) | Mean IC\( 50 \) (nM) ± SD |
|-----------|----------------|----------------|----------------|--------------------------|
| Chloroquine | 63.0           | 189.7          | 129.2 ± 45.2   |
| Quinine    | 102.7          | 278.2          | 185.2 ± 61.7   |
| Mefloquine | 10.7           | 24.5           | 16.6 ± 3.9     |
| Artesunate | 3.0            | 4.4            | 3.8 ± 0.5      |

To compare the parasites collected from these three southernmost provinces, the polymorphisms of the \( pfmdr1 \) gene in the parasites from Ranong, Chum phon, provinces along the Thai-Myanmar border, were also determined. Similar to previous studies, most of these parasites, especially those collected from Ranong, had the 184F allele and increased copy number of the \( pfmdr1 \) gene. In contrast to the \( pfmdr1 \) gene, all the study parasites contained the CQ-resistant genotype, the 76T allele.
found in all parasites collected from Yala. Similar to this previous study, nearly all parasites collected from three provinces of the Thai-Malaysia border, including Yala, contained the similar pfmdr1 genotype, the 86Y allele. The distribution of the pfmdr1 polymorphisms in the parasites from these three southernmost provinces of Thailand was different from those from Pahang, Peninsula Malaysia, containing the pfmdr1 N86 allele in most isolates [36]. Low variation of the parasite population in this area could be due to recent expansion of the local parasites with fewer introductions of the parasites with other genotypes in the area. Foreign migrant workers in this area were fewer compared to the Thai-Myanmar area, such as Ranong, because of political unrest.

All adapted P. falciparum isolates from Yala exhibited a CQ-resistant phenotype. These parasites were QN- and MQ-sensitive. In vitro drug susceptibility pattern of the adapted P. falciparum isolates in this study was similar to the results of the study by Runghishirunrat et al. [37]. Although the pfcrT 76T allele has been proved to be a key determinant for in vitro CQ resistance, the polymorphisms of pfmdr1 gene could modulate the level of CQ resistance [9,10]. Besides, the 86Y allele was also identified as the predictor of CQ treatment failure [38]. It has been shown that parasites with different resistant phenotypes and genotypes exhibited different levels of fitness which might explain the unique parasite structure of P. falciparum in the Thai-Malaysia border. The influence of parasites’ fitness was indicated when CQ-sensitive strains were re-emerging in some countries where CQ use was discontinued because of widespread CQ resistance [39,40]. Using allelic replacement technique, insertion of the 7G8, CQ-resistant alleles into CQ-sensitive strain, D10 resulted in the loss of parasites’ fitness [41]. In contrast, a recent study of clinical samples showed that the parasites with the pfmdr1 86Y and D1246 alleles had the fitness advantage over others [42]. Moreover, the parasites with the pfmdr1 86Y allele could produce a higher number of gametocytes [43] which would gain the advantage in term of transmission.

**Conclusion**

A nationwide implementation of a three-day ART instead of a two-day ART in combination with two-day MQ regimen has been started in Thailand since 2008 to overcome a low cure rate in some areas [1]. However, a new fixed dose ACT will inevitably be considered by the Ministry of Public Health in the near future. The present study showed that P. falciparum isolated from different areas along the international border of Thailand exhibited different resistant phenotypic and genotypic patterns. This information will be useful for anti-malarial drug policy in Thailand. New candidate drugs should be adopted at least based on their activity against these phenotypic and genotypic parasites in different areas of Thailand.

**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

MM and SL conceived of the study, participated in the design and coordination of the study and performed the statistical analysis. SI, PS, SA and ST carried out the field works. NSi performed molecular analysis. NSu carried out the in vitro cultivation and sensitivity test. All authors read and approved the final manuscript.

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