Distribution of Drug Resistance Genotypes in *Plasmodium falciparum* in an Area of Limited Parasite Diversity in Saudi Arabia


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**Abstract.** Two hundred and three *Plasmodium falciparum* isolates from Jazan area, southwest Saudi Arabia, were typed for *Pfcr*, *Pfmdr1*, *dhps*, and *dhfr* mutations associated with resistance to chloroquine, mefloquine, halofantrine, artemisinin, sulfadoxine-pyrimethamine, and the neutral polymorphic gene *Pfg*377. A large proportion (33%) of isolates harbored double mutant *dhfr* genotype (51*L*-59*C*-108*N*). However, only one isolate contained mutation *dhps*-437*G*. For *Pfcr*, almost all examined isolates (163; 99%) harbored the mutant genotype (72*C*-73*V*-74*I*-75*E*), whereas only 49 (31%) contained the mutant *Pfmdr1* genotype (86*N*-184*E*-1034*S*-1042*N*), 109 (66%) harbored the single mutant genotype (86*N*-184*E*-1034*S*-1042*N*), and no mutations were seen in codons 1034, 1042, and 1246. Nonetheless, three new single-nucleotide polymorphisms were detected at codons 182, 192, and 102. No differences were seen in distribution of drug resistance genes among Saudis and expatriates. There was a limited multiplicity (5%), mean number of clones (1.05), and two dominant multilocus genotypes among infected individuals in Jazan. A pattern consistent with limited cross-mating and recombination among local parasite was apparent.

**INTRODUCTION**

The Arabian Peninsula lies at the fringes of malaria endemicity, where successful control efforts have brought local transmission to a halt in many parts of this region. At the same time, limited foci in Yemen and southern Saudi Arabia remain malarious, with a high prevalence of drug-resistant *Plasmodium falciparum* parasites.1–6

In Saudi Arabia, malaria transmission is confined to southwestern regions (the Aseer and Jazan provinces), where *P. falciparum* is the prevailing species and *Anopheles arabiensis* is the main vector.7–11 However, malaria cases are still reported in different parts of the country, mostly brought by travelers from endemic sites in the south or expatriates from outside the country.1,12

Chloroquine was the drug of choice for the treatment of uncomplicated malaria cases for many years. However, the emergence and spread of chloroquine resistance (CQR)13–15 has lead to the introduction of sulfadoxine-pyrimethamine (SP) therapy, which is effective. Nonetheless, recently health authority in Saudi Arabia has adopted artemisinin combination therapy (ACT), consisting of artemisinin plus SP. A recent study has revealed high prevalence of *Pfcr*76*T* and *Pfmdr1*186*Y* mutations among *P. falciparum* parasites in Jazan.9 In addition, mutation *dhfr*59*R* was suspected; however, no data were presented on codons 51 and 108 or codons 436, 437, 540, and 581 on *dhps*, which are critical markers for pyrimethamine and sulfadoxine resistance and subsequent SP failure.

Here, we have extended the above findings and examined 16 single-nucleotide polymorphisms (SNPs) on *dhfr*, *dhps*, *Pfcr*, and *Pfmdr1* genes implicated in resistance to an array of antimalarial drugs, including SP, chloroquine, amodiaquine, artemisinin, and lumefantrine. Some of these genes have recently been suggested to have an antagonistic selective role.6,11 Therefore, the pattern of response of *P. falciparum* to different combination antimalarial therapy may be influenced by mutations in these genes, and their role in predicting response to combination therapy can be of paramount importance.

**MATERIALS AND METHODS**

**Study subjects.** Jazan region, southwest Saudi Arabia, is endemic for malaria, where the vast majority of the cases are caused by *P. falciparum* and *An. arabiensis* is the main vector. Malaria transmission occurs after the rainy season from November to March and the appearance of *Anopheles* mosquitoes. *P. falciparum* in the region was at one time susceptible to chloroquine; however, resistance emerged in the late 1990s,14 and mutations associated with CQR have escalated in the region.9 This finding prompted the change of treatment policy to artemisinin-based combination therapies (ACTs).18

The present study examined 203 samples obtained, with informed consent, from microscopy-confirmed *P. falciparum* malaria patients from 11 hospitals and polyclinics in Jazan (Figure 1). The majority of patients (163; 80%) were Saudi; 145 (89%) were residents of Jazan, and 18 (11%) were visitors from other parts of the country. The remaining 40 (20%) were expatriates: 18 (45%) were residents, and 22 (55%) were visitors. Most of the patients (85%) were males. Their ages ranged from 2 months to 80 years, the largest group being between 20 and 29 years (16%).

Finger prick blood samples were spotted onto filter paper (Whatman 3M, Polybags Ltd., Greenford, Middlesex, UK) and individually sealed in plastic envelopes. All patients who participated in the study signed a consent form, and the study was approved by the Ethics Committee at King Khalid University, Abha, Saudi Arabia.

**Dhfr, dhps, Pfcr, and Pfmdr1 genes.** *P. falciparum* DNA was prepared from filter paper samples of blood as described previously.19 Alleles of the *dhfr*, *dhps*, *Pfcr*, and *Pfmdr1* genes were amplified using two rounds of polymerase chain reaction (PCR) as described previously.1,12,19–22 The amplified fragment of each gene encompasses mutations associated with pyrimethamine resistance (*dhfr*-51, -59, -108, and -164), sulfadoxine resistance (*dhps*-436, -437, -540, and -581), CQR

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Prevalence of alleles of dhfr, dhps, Pfcr, and Pfmdr and the polymorphic control gene Pf377 among 165 P. falciparum isolates from Jazan, southwest Saudi Arabia

<table>
<thead>
<tr>
<th>Table 1</th>
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<tbody>
<tr>
<td>Prevalence of alleles of dhfr, dhps, Pfcr, and Pfmdr and the polymorphic control gene Pf377 among 165 P. falciparum isolates from Jazan, southwest Saudi Arabia</td>
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</table>

<table>
<thead>
<tr>
<th>dhfr alleles</th>
<th>N (%)</th>
<th>dhps alleles</th>
<th>N (%)</th>
<th>Pfcr alleles</th>
<th>N (%)</th>
<th>Pfmdr alleles</th>
<th>N (%)</th>
<th>Pf377 alleles (bp)</th>
<th>N (%)</th>
</tr>
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<tbody>
<tr>
<td>108N</td>
<td>60 (34)</td>
<td>437G</td>
<td>1 (0.56)</td>
<td>74M</td>
<td>2 (1)</td>
<td>86Y</td>
<td>51 (31)</td>
<td>269</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>108S</td>
<td>117 (66)</td>
<td>437A</td>
<td>178 (99.4)</td>
<td>74l</td>
<td>162 (99)</td>
<td>86N</td>
<td>118 (69)</td>
<td>289</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>51I</td>
<td>58 (33)</td>
<td>437A</td>
<td>178 (99.4)</td>
<td>75N</td>
<td>2 (1)</td>
<td>184F</td>
<td>159 (96)</td>
<td>310</td>
<td>49 (28)</td>
</tr>
<tr>
<td>51N</td>
<td>117 (67)</td>
<td></td>
<td></td>
<td>75E</td>
<td>162 (99)</td>
<td>184Y</td>
<td>5 (3)</td>
<td>331</td>
<td>82 (48)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>76K</td>
<td>2 (1)</td>
<td>184F</td>
<td></td>
<td>352</td>
<td>38 (22)</td>
</tr>
</tbody>
</table>

RESULTS

dhfr and dhps genotypes. Tables 1 and 2 show distribution of dhfr and dhps alleles and corresponding genotypes in Jazan among the 176 and 179 P. falciparum isolates examined for dhfr and dhps, respectively. For dhfr, mutations N51I and 108N were frequent, occurring at prevalences of 33% and 34%, respectively. However, other mutations, at codons 59R and 164I, associated with high-level SP resistance were not seen. Similarly, dhps mutations associated with SP resistance at codons 436, 437, 540, and 581 were not seen, with the exception of mutation 437G, which was detected in one isolate (Tables 1 and 2).

Wild-type dhfr (N51 C69 S108) and dhps (A437 K540) genotypes were predominant, existing at prevalences of 65.90% and 99.44%, respectively. However, single- (N108) and double-mutant (I51N108) dhfr genotypes were less prevalent at 1.14% and 32.95%, respectively, whereas the triple mutant (I51 R59 N108) associated with high-level pyrimethamine resistance was not seen in the region (Tables 1 and 2).

Pfcr genotypes. CQR-associated mutations in Pfcr were extremely high in Jazan area; 162 (99%) of 164 isolates successfully examined harbored the genotype (C72 V73 I74 E75 T90), and only 2 (1%) isolates carried the wild type (C72 V73 M74 N75 K76) (Tables 1–3).

Pfmdr alleles and genotypes. Genotyping of Pfmdr1 was completed for 165 P. falciparum isolates. We found mutations only in codons 86 and 184 and no mutations at codons 1034 and 1042. At codon 86, 118 (69%), 51 (30%), and 2 (1%) isolates harbored the wild-type allele (86N), the resistance allele (86Y), and mixed alleles (86N/86Y), respectively. For codon 184, 5 (3%), 159 (96%), and 1 (1%) carried the wild-type allele (184Y), the resistance allele (184F), and mixed alleles (184Y/184F), respectively (Tables 1 and 2). In addition, 0 of 46 isolates examined for codon 1246 were found to harbor a mutant allele, despite the fact that 13 and 38 of these isolates had mutation at codon 1246.

Furthermore, three new SNPs were detected: T306, T546, and T728. The T306C and T546G in codon 102, and T728G in codon 192. The first two SNPs are synonymous, and the last one is non-synonymous. Mutation T546G was more common, seen among the isolates examined. The multiplicity of infection was defined as the proportion of people who carry more than one allele (genotype) for any of the examined genes, and the minimum number of clones per infection was estimated as the largest number of alleles at any of the examined loci. 28 SPSS program (16.0.0) has been used to calculate odd ratio (OR), $\chi^2$ test, and $P$ value.
five isolates, compared with the other two mutations, which were each found in one isolate. This mutation has recently been reported in some P. falciparum isolates in India.31

Among the 163 isolates with complete sequence data, five (3%) isolates carried the wild genotype (N86, Y184, W186, S1034, N1042). However, 108 (65%) and 49 (30%) harbored single- (N86, L67, F184, W186, S1034, N1042) and double-mutant genotypes (Y86, L67, F184, W186, S1034, N1042), respectively (Tables 1–3).

**Distribution of resistance genotypes among Saudis and expatriates.** The majority of isolates (163; 80%) were obtained from Saudis: 145 (89%) were residents of Jazan, and 18 (11%) were Saudi visitors. In addition, 40 (20%) samples were collected from expatriates: 18 (45%) were residents, and 22 (55%) were visitors.

The risk of harboring a resistance strain of P. falciparum among Saudi and non-Saudi was equal (OR = 1), with 95% confidence interval (CI) at 0.458–2.182. No significant association was seen between harboring resistance strain and gender (χ² = 0.79), living status (χ² = 0.865), or nationality (χ² = 1 at P < 0.005). However, the only mutant allele in dhps gene was harbored by an expatriate. Similarly, the wild-type Pfcr allele was only carried by two expatriated visitors (Table 4).

**Pfg377 alleles and parasite diversity.** At least five Pfg377 alleles, varying in size between 269 and 352 base pairs, were detected. The difference between each of the two closest alleles is approximately 21 base pairs, which reflects variation in the number of amino acids repeat of region 3.23 The common allele (2,14 base pairs) varies in size between 269 and 352 base pairs, were each found in one isolate. This mutation has recently been reported in some P. falciparum isolates in India.31

The southwestern region of Saudi Arabia (Jazan) is a major malaria-endemic site,32 where chloroquine was previously the drug of choice for the treatment of malaria cases. In this area, P. falciparum remained sensitive to chloroquine up until the late 1990s,15 unlike neighboring malaria-endemic sites, such as Yemen and the closest east African countries,3,33,34 where CQR was common. The health authority in Saudi Arabia has lately changed the first line of treatment for malaria to ACT: SP plus artesunate.

Limited studies have examined drug resistance genes in the Jazan area and shown the presence of mutant alleles of some drug resistance genes: Pfcr:76T, Pfmdr1:86Y, and dhfr:59R.9,12 The present study has extended the above findings and analyzed 16 SNPs in four genes involved in resistance to commonly used antimalarial drugs. dhfr and dhps mutations associated with SP resistance existed at low prevalence in Jazan area; however, mutations in Pfcr and Pfmdr1 genes linked with chloroquine, amodiaquine, mefloquine, and possibly artemisinin35 are common, which is in agreement with a recent report from the area.33

The low prevalence of dhfr and dhps implies that the current use of SP in Jazan may be imposing only weak selection on these genes or that there has been insufficient time for selection to leave a molecular signature. Evidence of selection is generally found in dhfr earlier than dhps36,37; thus, it is likely that we may be seeing the initial phase of SP resistance in Jazan. An additional point that supports this hypothesis is that almost all the resistance dhfr genotypes consist of

**DISCUSSION**

The mean number of clones per infection (1.05) was very close to one. In addition, two major haplotypes (multilocus genotypes with identical alleles for all loci), haplotypes 4 and 5, existed at prevalences of 20% and 18%, respectively, among the 93 P. falciparum isolates with single-clone infection (Table 3).

<table>
<thead>
<tr>
<th>Table 2</th>
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<tr>
<td><strong>Prevalence of dhfr, dhps, pfcr and pfmdr genotype among 165 P. falciparum isolates in Jazan, southwest Saudi Arabia</strong></td>
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</table>

<table>
<thead>
<tr>
<th>dhfr genotypes</th>
<th>dhps genotypes</th>
<th>Pfcrt genotypes</th>
<th>Pfmdr1 genotypes</th>
</tr>
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<tbody>
<tr>
<td>Wild type (NCIS)</td>
<td>116 (65.7)</td>
<td>Sensitive (SAKA)</td>
<td>177 (99.4)</td>
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<tr>
<td>Single mutant (NCNI)</td>
<td>2 (1.14)</td>
<td>Single mutant (SGKA)</td>
<td>1 (0.56)</td>
</tr>
<tr>
<td>Double mutants (ICN)</td>
<td>58 (33.9)</td>
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**Table 3**

| Multi-locus haplotypes of 93 P. falciparum isolates with single-clone infection in Jazan area, western Saudi Arabia |

<table>
<thead>
<tr>
<th>Haplotype</th>
<th>dhfr</th>
<th>dhps</th>
<th>Pfg377</th>
<th>Pfcrt</th>
<th>Pfmdr1</th>
<th>Frequency</th>
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Total 93
double mutants (I31, N108) rather than the highly resistance triple mutant (I31, R59, N108) found in Africa and Southeast Asia where SP resistance is well-established.36,39 Thus, it is possible that highly resistant genotypes have not spread in this region. A limited study carried out in 2005 in the Jazan area has previously reported the presence of dhfr-59R allele.12 However, this allele was not detected in the current study. This discrepancy is unexpected, because the dhfr-59R allele is associated with high-level resistance to pyrimethamine.22 SP has been used in Jazan for sometime as a second line to chloroquine, and the above allele is expected to be under favorable selection in the face of drug pressure. Therefore, the small sample size (N = 19) analyzed by Al-Harthi12 may not have been representative of the Jazan parasite population, and the two isolates with 59R alleles may have been obtained from expatriates with asymptomatic chronic infection who acquired it outside Jazan; it is known to be capable of lasting for some months.30 Saudi Arabia is at great risk of imported malaria because of the large number of expatriate workers and the millions of annual visitors from malaria-endemic countries, for Hajj and Omrah.7. Additional analysis of microsatellite loci flanking the dhfr and dhps genes can indicate whether the mutant dhfr genotype in Jazan has evolved locally or shows close similarity to the common high-level resistance lineage seen in southeast Asia and Africa.38,39 This finding is of particular importance, because the only isolate that carried the mutation dhps 437G, which is associated with SP failure, was seen in an expatriate (Table 4).

Nonetheless, effective management of malaria outbreaks at health centers and clinics in Jazan using artesunate plus SP (ACT) can currently still control imported malaria and restrain escalation of drug resistance. However, the presence of a single mutant lineage carrying mutation 437 is alarming, because this mutation has been linked to high rate of SP failure in many sites.22 Continued molecular surveillance and in vivo drug efficacy assessments are recommended to guide appropriate policy revisions before widespread therapeutic failure.

High prevalence of the Pfcr1-resistance genotype (99%) seen among P. falciparum parasites in Jazan reflects the high level of CQR selection. The only mutant Pfcr1 genotype seen (C76, I74, E75, T58) is similar to the common genotype in Africa CVIET, which originated in Southeast Asia.41 This finding is not surprising in view of the high rate of expatriates and pilgrims from Asia and Africa. Analysis of microsatellites flanking the Pfcr1 gene in Jazan will shed light on its genetic background and whether it has evolved locally or not.39

The change from chloroquine to artemisinin + SP as the first-line antimalarial in Jazan is expected to decrease the CQR genotype and restore the chloroquine wild-type allele within the parasite population. This occurrence has been documented consistently after withdrawal of chloroquine in many African countries, such as Malawi,42 Tanzania,43 and Kenya.44 Therefore, it was unexpected to find Pfcr1-K76T at fixation. The persistence of the Pfcr1-K76T allele suggests an ongoing use of chloroquine or related drugs such as amodiaquine45 because of the recent shift to ACT,12 which can lead to selection of the mutant genotype. In addition, chloroquine, although not used for treatment of falciparum malaria, can be used for infections that are thought to be P. vivax but are actually unrecognized mixed infections or misdiagnosed P. falciparum infections.46 A large number of expatriates from the Indian subcontinent may import P. vivax infection.

Polymorphisms in the Pfmdr1 alleles (N86Y, Y184F, S1034C, N1042D, and D1246Y) may alter parasite responses to many antimalarial drugs, including chloroquine, quinine, mefloquine, and artemisinin.35,47 Mutations at codon 86 have been associated with CQR,35,47 whereas mutations at codons 184, 1034, 1042, and 1246 have been implicated to varying degrees in resistance to mefloquine and artesunate.35,47,50 An increased association between artesunate-mefloquine failure and a mutation at codon 184 has been seen in P. falciparum parasites in Cambodia.51 However, it is unlikely that the high frequency of mutations at codon 184 in the Jazan area is linked to mefloquine resistance, because this drug has not been in common use. A possible explanation is that the 184F allele has been driven by the high rate of CQR in the area.

A correlation between CQR and the Pfmdr1-N86Y mutation is well-established, because the Pfmdr1-N86Y mutation in conjunction with the Pfcr1-K76T mutation yields enhanced levels of resistance to chloroquine.31,34 However, we found fewer parasites with Pfmdr186Y than expected as Pfcr76T reached fixation. Similarly, findings have been reported from other sites, and it has been postulated that Pfmdr1 N86Y mutation may confer a compensatory advantage for coping
with chloroquine pressure, which may vary in different parasite populations.\textsuperscript{31,52}

It has recently been suggested that some antimalarial drugs exert opposite directional selection on parasite genotypes.\textsuperscript{16,53} For example, artemisinin-lumefantrine (AL) and amodiaquine (AQ) exert opposite within-host selective effects on the Pfmdr1 genes of \textit{P. falciparum}.\textsuperscript{16} Similarly, the PfK76T mutation may enhance \textit{P. falciparum} susceptibility to lumefantrine\textsuperscript{17} and thus, increase the benefits of using AL in areas affected by CQR \textit{P. falciparum} malaria, such as Jazan. Therefore, the current use of ACT in Jazan may be exerting a novel pressure on the local parasites to select for alleles Pfmdr1 86N 184F 1246D and Pfcr74M 75N 76K,\textsuperscript{53} some of which are currently rare in Saudi Arabia; however, the wild-type pfmdr1-1246D is at fixation, and the mutant form was not seen in neighboring countries such as Iran.\textsuperscript{54,55} Whether the prevalence of the wild-type Pfmdr1 mutations will change under increasing artemisinin pressure will be of considerable interest in the future. However, currently, the apparent effectiveness of SP should protect artemisinin and reduce effective selective pressure.

The observed low genetic diversity of the \textit{P. falciparum} in Jazan area probably reflects the impact of sustained control efforts, where limited transmission can restrict the gene pool. This finding is revealed in the low complexity (concurrent genotypes) of infection, where almost 95\% of infected patients carried a single clone and only 5\% are infected with multiple clones. Here, we have examined one polymorphic gene (pgf377); certainly, the addition of more polymorphic markers, such as msp-2, would have increased the rate of multiplicity. However, this increase is expected to be significantly higher because of the low transmission level and limited outcrossing in Jazan, which is evident by the occurrence of linkage disequilibrium. The level of multiplicity seen in Jazan is lower than the level in an area of low and seasonal transmission such as eastern Sudan, where the multiplicity of infection is approximately 20–40\% and the mean number of clones per infection is 1.3.\textsuperscript{56}

Thus, the markedly low level of diversity seen in Jazan is rare and seen typically in limited endemic sites such as island populations in Papua New Guinea and the Solomon Islands.\textsuperscript{57} The low within-host multiplicity can have profound effect of evolution of drug resistance. It affects both the strength of advantageous selection of resistance genotype in the presence of drug and the disadvantageous selection (fitness cost) in the absence of resistance.\textsuperscript{58,59} In addition, the low genetic diversity can result in limited opportunities for crossing and recombination to build up or break down existing multilocus drug resistance genotypes.\textsuperscript{60} In such areas, mutations associated with antimalarial drug resistance tend to reach fixation.\textsuperscript{61} Thus, it may take longer for the dominant Pfcr haplotype in Kingdom of Saudi Arabia to lose its grip in the absence of chloroquine pressure compared with areas with high transmission such as Africa. The absence of mutations in Pflliplas in Jazan, which are already present in east Africa and Yemen, is a possible further illustration of such a low gene flow.

In summary, the present data provide baseline information on the prevalence of \textit{P. falciparum} drug resistance-associated SNPs and highlight the low level of genetic diversity in the \textit{P. falciparum} population in the Jazan area of western Saudi Arabia. Surveillance of molecular markers of drug resistance should be an integral part of the planned malaria eradication programs; therefore, the resistance dynamics can be assessed, and the most effective treatment can be selected.

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