**Abstract**

**Purpose:** To determine the frequencies of important allelic variants and their haplotype frequencies of the gene among Jordanian population and to compare findings with those reported for other ethnic groups.

**Methods:** Genotyping of ABCB1 (C1236T, G2677T/A and C3435T) was carried out on unrelated healthy Jordanian subjects. Different allelic variants were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The haplotype frequencies of these three SNPs were analyzed and compared them with those of other reported populations. Haplotype frequencies were calculated using Golden Helix Tree software and Linkage disequilibrium was represented by D'.

**Results:** ABCB1 C3435T allele frequencies for C allele and T allele were 0.57 and 0.43, respectively. For ABCB1 G2677T/A the allele frequencies for G allele, T allele, and A allele were 0.65, 0.32 and 0.0, respectively. As for ABCB1 C1236T, its allele frequencies were 0.65 for C allele and 0.35 for T allele. C1236T, G2677T/A, and C3435T SNPs were expected to be structured in 8 different haplotypes with G-C-C (37.6.0 %), T-T-T (18.6 %), G-C-T (14.3 %) and T-T-C (12 %) that were most prominent. The haplotype frequency distribution of our study group was found to be significantly different from those of Chinese, Indian, Japanese, African and Caucasian (p < 0.0001) and resemble Ashkenazi Jewish and Slovenian populations (p > 0.05).

**Conclusion:** In addition to earlier studies, the findings of the current study provide evidence that suggest the use of genetic polymorphisms of ABCB1 SNPs as markers for ethnicity and ancestral origin. The analysis of haplotype and genotype can be useful in identifying the relation between ABCB1 polymorphism, disease susceptibility and drug disposition.

**Keywords:** Genotype, Allele, MDR1, ABCB1, Polymorphism, Haplotype frequencies

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**INTRODUCTION**

P-glycoprotein (P-gp), and the product of the multidrug resistance (MDR1) gene (recently renamed ABCB1) plays an important role in the bioavailability of a wide variety of drugs and are involved in drug-drug interaction in humans [1]. ABCB1 is highly polymorphic and a number of mutations have been documented in various ethnic populations [2]. Recently, genetic variations of ABCB1 gene have been studied very extensively, and over 50 single nucleotide...
polymorphisms (SNPs) have been reported [1,3]. The allelic frequency of ABCB1 SNPs varies widely among different ethnic groups [2,4]. Among many variants, C3435T (rs1045642) in exon 26 (Ile1145Ile); G2677T/A (rs2032582) in exon 21 (Ala893Ser/Thr) and C1236T (rs1128503) in exon 12 (Gly412Gly) are more frequent than other SNPs [5] and have been shown to affect the expression and function of P-gp [6-8]. These three SNPs have been the focus of many pharmacokinetic and disease association studies with controversial results [9]. The variant alleles of the three most common coding SNPs, at nucleotides 1236, 2677 and 3435 are in high Linkage disequilibrium as has been commonly found in multiple studies [4,9], and most haplotype analysis were carried out using these three SNPs. Kim et al named the haplotype 1236C, 2677G, 3435C as ABCB1*1, and the mutant alleles haplotype 1236T, 2677T, 3435T, was named as ABCB1*2 [8].

Haplotype analysis, in addition to the customary analysis of SNPs, may play an important role in the identification of genetic variations between ethnic groups. In addition, the functional effects of P-gp activity may also be related to haplotypes in the ABCB1 gene. The frequencies of the important allelic variants in ABCB1 genes have been extensively studied in many ethnic groups. In the present study, we report the allele frequencies of ABCB1 C1236T, G2677T/A and C3435T SNPs and their haplotype in a sufficiently large sample of apparently healthy unrelated Jordanian population. To our knowledge, it is the first haplotype frequency study of the Jordanian population reported to date.

While native Jordanians are mostly descended from people of villagers and Bedouin descent originating in the Arabian Peninsula [10], ethnically, the Jordanians represent a mixed stock. Most of the population is Arab (approximately 98 %) while 1 % of the population is Armenian, and another 1 % is Circassian. There are also small Kurd, Druze, and Chechen minorities [11].

EXPERIMENTAL

Subjects

Three hundred and thirty nine (339) apparently healthy unrelated Jordanian subjects were included in this study after detailed explanation of the purpose of the study followed by obtaining written informed consent for genetic analysis from all of them. The participants had an average age of 46.1 ± 15 years and majority of them were men (n = 235, 69 %). The study was approved by local Research Ethics Committees of the Jordan University Hospital (approval reference number M/C/A/111/1519, TH/F/3/1/1945 and TH/F/3/1/2046), the WMA declaration of Helsinki was followed [12].

From each subject, 1 ml of blood was collected. Genomic DNA was isolated from the blood using Wizard Genomic® (DNA purification kit) (Promega Corporation, USA). The isolated DNA samples were prepared for genotyping.

Genotype and haplotype analysis

Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) were used to identify different SNPs of ABCB1 (C1236T, G2677T/A and C3435T). Primers utilized, PCR annealing conditions and restriction enzymes are summarized in Table 1.

The findings of PCR-RFLP were validated as follows:

Table 1: Primer sequences in different SNPs and restriction enzymes used

| ABCB1 SNPs | Primers used | Annealing temperature (°C) | Restriction enzyme* |
|------------|--------------|---------------------------|-------------------|
| C1236T    | Forward: ctcgaaaagaagtaaggtaca  <br>Reverse: atctcaccatcccctctgtg | 58 | HaeIII |
| G2677T/A  | Forward: tttagtttgactcaccttcgg  <br>Reverse: ggacacctatagcctgcaaaaca | 60 | BanI, Rsal |
| C3435T    | Forward: gtaacttggcagtttcagtg  <br>Reverse: ataaacagcctgggagc<atg  <br>Reverse: ataaacagcctgggagc<atg | 56 | DpnII |

*PCR products were digested with a restriction enzyme that could distinguish between genotypes and was chosen using the website http://tools.neb.com/NEBcutter2/index.php
(1) PCR is sensitive to reagents contaminated with foreign DNA. A negative control contained all PCR components except the DNA template was run simultaneously to rule out contaminated reagents;

(2) Around 15% of all samples were repeated to confirm findings of the PCR-RFLP;

(3) The PCR-RFLP results of 10% of samples were confirmed for by direct DNA sequencing using BigDye Terminator Cycle Sequencing on 3730xl DNA sequencer (Macrogen® Co., Korea).

Statistical analysis

Allele and genotype frequencies for different alleles were estimated from the results of the above PCR-RFLP test. This estimation was carried out as earlier reported [13]. Genotype and allele frequency were matched to expectation by Hardy-Weinberg Equilibrium; differences in allele frequencies between Jordanians and other ethnic populations were assessed using Chi square test. Haplotype was analyzed using Helix Tree Genetics Analysis Software, Golden Helix Inc. P < 0.05 was considered statistically significant for population comparisons.

Linkage disequilibrium was calculated using equation [14] and quantified by D’ and r² values, also Linkage disequilibrium were calculated using MIDAS software [15].

RESULTS

ABCB1 SNPs frequencies

The frequencies of ABCB1 C1236T, G2677T/A and C3435T genotype for the 339 subjects are summarized in Table 2. Using Hardy-Weinberg equilibrium (H-W) there was no significant difference between the findings of the current study and H-W expectation (p > 0.05, Chi-Square) (Table 2). Not all samples were successfully analyzed for the three SNPs because either we ran out of sample (n = 6), failure of DNA extraction (n = 1), or failure of PCR (n = 4).

ABCB1 haplotype

The most frequent haplotypes are listed in Table 3. Linkage disequilibrium was described by D’; the standardized, pair wise Linkage disequilibrium value D’ was calculated for each pair of markers. In the current study, loci 2677 and 3435 show relatively strong Linkage disequilibrium (Lewontin’s coefficient [D’] = 0.765; r² = 0.426), However, 1236-2677 and 1236-3435 show weak Linkage disequilibrium ([D’] = 0.303; r² = 0.087 and [D’] = 0.319; r² = 0.091 respectively). Table 4 shows T-allele frequencies among different ethnicities while the haplotype frequencies among different ethnicities are listed in Table 5.

| Tested SNP | N   | Observed frequency (%) | Predicted frequency (H-W) (%) | p-value |
|------------|-----|------------------------|-------------------------------|---------|
| ABCB1 3435 |     |                        |                               |         |
| CC         | 112 | 33.2                   | 32.6                          | 0.56    |
| CT         | 160 | 47.5                   | 49.1                          |         |
| TT         | 65  | 19.3                   | 18.3                          |         |
| ABCB1 2677 |     |                        |                               |         |
| GG         | 130 | 39.25                  | 42                            |         |
| GT         | 164 | 50.75                  | 45.6                          | 0.11    |
| GA         | 0   | 0                      | 0                             |         |
| TT         | 35  | 10                     | 12.4                          |         |
| AA         | 0   | 0                      | 0                             |         |
| ABCB1 1236 |     |                        |                               |         |
| CC         | 142 | 29.8                   | 35.2                          |         |
| CT         | 154 | 59.2                   | 48.2                          | 1.00    |
| TT         | 42  | 11                     | 16.6                          |         |

Total number of subjects was 339. Numbers of genotypes do not add up to 339 because: ran out of sample, failure in DNA extraction, and/or failure of PCR.
### Table 3: Haplotype frequencies among Jordanians

| Haplotype * | EM Probability | CHM Prob |
|-------------|----------------|----------|
| CGC         | 0.376          | 0.276    |
| TTT         | 0.186          | 0.11     |
| CGT         | 0.143          | 0.16     |
| TTC         | 0.12           | 0.11     |
| TGT         | 0.06           | 0.10     |
| TGC         | 0.06           | 0.11     |
| CTT         | 0.03           | 0.06     |
| CTC         | 0.018          | 0.08     |

Haplotypes order: C3435T-G2677T/A-C1236T; CHM: Composite Haplotype Method; M: Expectation Maximization

### Table 4: Comparison of the T-allele frequencies of ABCB1 reported from different ethnic populations

| Population          | N    | 3435 (T) | 2677 (T/A) | 1236 (T) | References |
|---------------------|------|----------|------------|----------|------------|
| Jordanian           | 339  | 0.43     | 0.32/NA    | 0.35     | Current study |
| Caucasians (USA)    | 99   | 0.566    | 0.434/0.036| 0.459    | [16]        |
| German              | 188  | 0.52     | Not reported| 0.38     | [5]         |
| Polish              | 139  | 0.522    | 0.414/0.576| 0.414    | [17]        |
| Slovenian           | 355  | 0.47     | 0.40/NA    | 0.38     | [18]        |
| Asians              |      |          |            |          |            |
| Japanese            | 154  | 0.406    | 0.406/0.166| 0.656    | [16]        |
| Chinese             | 207  | 0.347    | 0.364/0.114| 0.638    | [19]        |
| Indian              | 87   | 0.632    | 0.598/0.069| 0.672    | [20]        |
| Saudi Arabia        | 189  | 0.422    | 0.40/0.008 | 0.437    | [21]        |
| Moroccos            | 100  | 0.355    | 0.275/NA   | 0.325    | [22]        |
| African-Americans   | 99   | 0.202    | 0.1/0.005  | Not reported | [23] |
| Brazilian (white)   | 106  | 0.45     | 0.38/0.01  | 0.41     | [24]        |
| Brazilian (black)   | 100  | 0.31     | 0.18/0.01  | 0.33     | [24]        |
| Ashkenazi Jewish    | 101  | 0.50     | 0.41/NA    | 0.42     | [25]        |

### Table 5: Comparison of haplotype frequencies of ABCB1 reported for different ethnic populations

| Population          | Sample | CGC (%) | TTT (%) | Others (%) | P-value* | References |
|---------------------|--------|---------|---------|------------|----------|------------|
| Jordanian           | 339    | 37.6    | 18.6    | 43.4       |          | Current study |
| Caucasian           |        |         |         |            |          |            |
| Slovenian           | 355    | 40.1    | 23.1    | 36.8       | 0.156    | [18]       |
| French              | 222    | 44      | 35.3    | 20.7       | < 0.001  | [26]       |
| Turkish             | 107    | 25      | 33.7    | 41.3       | 0.03     | [27]       |
| Saudi Arabian       | 189    | 48.8    | 35.5    | 15.7       | < 0.00001| [21]       |
| Moroccan            | 100    | 53      | 21      | 26         | 0.034    | [22]       |
| African American    | 99     | 43.6    | 8.7     | 47.7       | 0.036    | [23]       |
| Brazilians (black)  | 100    | 58.9    | 15.8    | 28.3       | < 0.001  | [24]       |
| Asian               |        |         |         |            |          |            |
| Chinese             | 207    | 16.8    | 35.7    | 47.5       | < 0.0001 | [19]       |
| Indian              | 68     | 17.56   | 31.38   | 51.06      | < 0.0001 | [28]       |
| Korean              | 232    | 18.6    | 32.2    | 49.2       | < 0.0001 | [29]       |
| Ashkenazi Jewish    | 101    | 31.7    | 23.6    | 44.7       | 0.57     | [25]       |

*P-values were calculated using: http://www.danielsoper.com/statcalc3/calc.aspx?id=58
DISCUSSION

Several lines of evidence suggest a role for the multidrug resistance gene ABCB1/MDR1 to disease susceptibility, such as Crohn’s disease and cancer [30]. MDR1 is highly expressed in drug-resistant cancer cells. Several chemotherapeutic agents are affected by MDR1 genetic polymorphism mainly platinum-based chemotherapy response in lung cancer [30]. The need to study these different polymorphisms and haplotypes has been necessary to evaluate the inter-individual variation in disease progression, response and treatment especially chemotherapeutic agents.

ABCB1 is a highly polymorphic gene, and three SNPs that were extensively studied in healthy populations as well as in different clinical conditions [2,7,30] were investigated in this research. The frequencies of ABCB1 allelic variants differ widely among different ethnic groups [4,8].

The frequency of the ABCB1 C1236T, G2677T/A and C3435T mutant alleles among the Jordanian population was 35 %, 32 % and 43 % respectively, which is in the range comparable with other Caucasians; Americans, German and Turkish populations. On the other hand, the frequencies among Jordanians are quite different from those reported for Japanese, Chinese African American, and Moroccan. Table 4 is a comparison between the Jordanian population SNPs frequencies from the current study and other ethnic populations.

Since the frequency of the polymorphism at 3435 varies according to ethnicity, it is no surprise that the haplotype which carries this SNP shows a similar pattern. It is clear that people of African origin carry predominantly the wild-type (GCC) allele and not the haplotype allele (TTT) [6,23]. In Caucasian people, the frequency of GCC and TTT alleles is approximately the same [6,23,26]. It is interesting that the TTT haplotype is the predominant genotype among Asian and Indian populations. Table 5 summarizes the haplotype distribution of ABCB1 among healthy individuals in different races.

Regarding haplotype frequencies among Jordanian population, 8 different haplotypes appeared in our analysis, the most frequent haplotypes were CGC (37.6 %), TTT (18.6 %), CGT (14.3 %), TTC (12 %) the other haplotypes had frequencies less than 6 % (Table 3). These four most frequent haplotypes among Jordanian population were also reported to be the four most frequent haplotypes among Turkish, Saudi Arabia and Jewish populations [21,25,27]. The Wild type CGC is the predominant haplotype among Jordanian as is the case among other Caucasian population [4], but not among Asian, Japanese and African populations [19,23,28], in which TTT is the predominant haplotype.

When considering the two haplotypes CGC and TTT, the reported literature reveals that Slovenian and Jewish Populations were the closest to the Jordanians [25,27]. These three populations had CGC as the most frequent haplotype followed by TTT, then by CGT (Table 5). A new study that has been published among Saudi Arabian population regarding haplotype frequencies [21], revealed that CGC and TTT are the predominant haplotypes with higher frequencies compared to Caucasian and Jordanian in the present study (Table 5). However, the most frequent haplotypes in Saudi Arabian and Moroccan populations are similar to our study but significantly with different frequencies [21,22].

Linkage disequilibrium has been reported between the most common polymorphisms found in ABCB1 at positions C1236T, G2677T/A, and C3435T [4,8,27]. Of the synonymous SNPs, two (C1236T and C3435T) were linked to a non-synonymous SNP (G2677T/A, Ala893Ser) and occurred in 62 % of the European Americans, but in only 13 % of the African Americans tested [8]. Additionally, previous research reported statistically significant Linkage disequilibrium between all C1236T, G2677T/A, and C3435T SNPs [4,27]; However, our results indicated that only loci 2677 and 3435 showed relatively strong Linkage disequilibrium (Lewontin’s coefficient [D'] = 0.76 ; r² = 0.42), as was also observed [18,27].

Limitation of the study

There are more than 50 known SNPs for MDR1 gene and most studies only analyzed these three SNPs as they are considered the most frequent SNPs in most populations and are known to influence the activity of P-glycoprotein. Only 3 SNPs were analyzed for haplotyping in this study which may limit the interpretation of the results. Furthermore, the SNPs were genotyped by PCR-RFLP and only 10 % of the samples were sequenced to confirm the result when a better Linkage disequilibrium (Lewontin’s coefficient [D'] = 0.76 ; r² = 0.42), as was also observed [18,27].

CONCLUSION

The current study has successfully determined common allelic variants in ABCB1 among Jordanian population, some of which are being
reported for the first time among the population. The frequencies obtained are comparable to data previously reported in other populations of Caucasian origin but differ from that observed in African and Asian populations. Furthermore, haplotype frequencies are different from those among African, Asian and other populations, but resemble those among Jewish and Slovenian population. The findings of the current study, in addition to earlier studies, provide evidence to suggest the use of genetic polymorphisms of ABCB1 SNPs as markers for ethnicity and ancestral origin.

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