

Distribution of *CYP2D6* polymorphism in the Middle Eastern region

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Cytochrome P450 2D6 (*CYP2D6*) is an important drug-metabolizing enzyme involved in the pharmacokinetic metabolism of drugs. *CYP2D6* gene is highly polymorphic, and the combination of its different alleles yields different phenotypes including extensive metabolizer (EM), intermediate metabolizer (IM), poor metabolizer (PM), and ultrarapid metabolizer (UM). Genotyping of the important alleles for this gene in different ethnicities is of particular importance for assessing the efficacy of various drugs. In this study, we reviewed the *CYP2D6* allele and phenotype frequencies predicted from the genotypes of *CYP2D6* in the Middle East area. Regardless of different ethnicities, the *CYP2D6**41 allele frequency was shown to be higher than that of other reduced functional alleles. In addition, *CYP2D6**4 was the most frequent nonfunctional allele in all studied populations in the Middle East. Taken together, our findings illustrated that the frequencies of PM or IM alleles and different genotypes harboring these alleles are relatively high in the Middle Eastern countries. Therefore, the study of *CYP2D6* alleles for each patient to detect those that are at risk is of great importance to prevent adverse drug reactions through individualization therapy.

Key words: Allele frequency, cytochrome P450 2D6, Middle East

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INTRODUCTION

Understanding the genetic pathways involved in pharmacokinetics and pharmacodynamics of the drugs can have a substantial effect on the personalized treatment of the patients.^[1] Differences in patients' response to drug treatment are partly due to individual differences in genetic constitution such as genes encoding drug-metabolizing enzymes.^[2,3] Cytochrome P450 2D6 (*CYP2D6*) is one of the most important drug-metabolizing enzymes implicated in the metabolism of many clinical drugs such as antipsychotic drugs, antiarrhythmic agents, tricyclic antidepressants, β -blockers opioids, and anticancer drugs.^[4,5] The *CYP2D6* is a highly polymorphic gene, with more than 100 allelic variants being

currently reported for.^[6] The combination of different alleles yields different phenotypes such as extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) which have normal, reduced, and no activity of the enzyme, respectively.^[7,8] The doubling of the gene that produces an enzyme with increased activity is also called the ultrarapid metabolizer (UM).^[9,10] Interindividual differences in the kinetic characteristics of the drugs are partly attributed to the presence of alleles with altered activity.^[11] Human variability in the kinetics of *CYP2D6* substrates has been shown for different compounds metabolized extensively (>60%) by this polymorphic enzyme.^[12]

Due to the effect of the *CYP2D6* enzyme activity on drug metabolism, genetic studies of the gene in different

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populations are needed to determine the frequency of alleles in each ethnic group. This will help choose the effective treatment for the patients based on the genotype. The current study reviews the allele and genotype frequencies of CYP2D6 in the Middle East region. We searched in PubMed and Google Scholar from 1996 to 2017 using the combination of keywords such as CYP2D6, allele, and frequency plus the name of each country in the Middle East region. All studies reported CYP2D6 allele and genotype frequencies in different Middle Eastern countries including Saudi Arabia,^[13,14] Egypt,^[15-21] United Arab Emirates (UAE),^[22,23] Iran,^[24-27] Jordan,^[28] Syria,^[29] and Turkey^[30-45] performed on healthy unrelated controls or patient samples were reviewed in this article. Overview of the studies evaluated in this review is listed in Table 1, showing the number of studies in each geographic region, number and type of

samples (healthy or patients), list of alleles considered, and their frequency in each study.

DISTRIBUTION OF THE CYTOCHROME P450 2D6 ALLELIC FREQUENCIES IN THE MIDDLE EAST

In the present study, alleles were assigned according to the nomenclature for human CYP2D6 alleles.^[46] The examined alleles were classified according to their function labeled with functional, reduced, nonfunctional, and duplications. The average frequency of the CYP2D6 alleles in each country is shown in Figure 1.

The two functional frequent alleles, 2D6*1 or *2, were considered in some previous studies if no variants were found.^[47] However, now, the *1 and *2 alleles can be

Table 1: Overview of the studies evaluated in this review

Country (reference)	Number of individuals (n)	Subject type	Functional alleles		Reduced functional alleles			Nonfunctional alleles				Duplications 2xx
			1*	2*	10*	17*	41*	3*	4*	5*	6*	
Saudi Arabia ^[14]	101	Healthy	79.1	N/A	3	3	N/A	N/A	3.5	1	N/A	10.4
Saudi Arabia ^[13]	192	Healthy	78.4	N/A	N/A	N/A	18.4	0	N/A	N/A	0	N/A
Egypt ^[15]	21+22	Healthy + bladder cancer	47.7	N/A	N/A	N/A	N/A	52.3*			N/A	N/A
Egypt ^[16]	27+37	Healthy + bladder cancer	54.7	N/A	N/A	N/A	N/A	45.3*			N/A	N/A
Egypt ^[17]	429+123	Healthy + hypertensive cases	85.1	N/A	N/A	N/A	N/A	14.9*			N/A	N/A
Egypt ^[18]	11+32	Healthy + acute leukemia	53.5	N/A	N/A	N/A	N/A	N/A	46.5	N/A	N/A	N/A
Egypt ^[20]	308	Healthy fertile and infertile	74.4	N/A	N/A	N/A	N/A	N/A	25.6	N/A	N/A	N/A
Egypt ^[21]	29+30	Healthy + chronic organophosphate exposed patients	78	N/A	N/A	N/A	N/A	N/A	22	N/A	N/A	N/A
Egypt ^[19]	29+40	Healthy + acute organophosphate exposed patients	81.9	N/A	N/A	N/A	N/A	N/A	18.1	N/A	N/A	N/A
Iran ^[25]	100	Healthy	43.5	32	9	0	N/A	N/A	12.5	3	N/A	N/A
Iran ^[26]	100	Healthy	90	N/A	N/A	N/A	N/A	0.5	9	N/A	0.5	N/A
Iran ^[27]	101	Breast cancer	63.4	N/A	N/A	N/A	N/A	N/A	36.6	N/A	N/A	N/A
Iran ^[24]	300	Healthy	68.2	N/A	31.8	N/A	N/A	N/A	0	N/A	N/A	N/A
Turkey ^[34]	80+32	Healthy + SLE patients	85.3	N/A	N/A	N/A	N/A	0.4	14.3	N/A	N/A	N/A
Turkey ^[41]	53	Ankylosing spondylitis patients	84	N/A	N/A	N/A	N/A	N/A	16	N/A	N/A	N/A
Turkey ^[45]	100	Healthy	69	N/A	14.5	N/A	N/A	1	10	3	2.5	N/A
Turkey ^[44]	55+132	Healthy + epileptic children patients	81.8	N/A	N/A	N/A	N/A	0.8	17.4	N/A	N/A	N/A
Turkey ^[43]	30+60	Responsive and nonresponsive FMF patients	55	N/A	N/A	N/A	N/A	4.2	15.8	2.5	22.5	N/A
Turkey ^[42]	140+155+94	Healthy + ALL + AML	82.8	N/A	N/A	N/A	N/A	1.3	15.9	N/A	N/A	N/A
Turkey ^[35]	249	Turkey with symptoms of arthritis, sacroiliac, joint and back pain	87.8	N/A	N/A	N/A	N/A	N/A	12.2	N/A	N/A	N/A
Turkey ^[32]	160	Healthy	81	N/A	N/A	N/A	15	N/A	N/A	N/A	N/A	N/A
Turkey ^[31]	128+135	Healthy + breast cancer patients	66.3	N/A	N/A	N/A	N/A	N/A	33.7	N/A	N/A	N/A
Turkey ^[38]	52+100	Healthy + ankylosing spondylitis patients	83.9	N/A	N/A	N/A	N/A	N/A	16.1	N/A	N/A	N/A
Turkey ^[33]	140	Healthy	83.6	N/A	N/A	N/A	N/A	2.5	13.9	N/A	N/A	N/A
Turkey ^[40]	404	Healthy	37.06	35.3	6.06	1.11	N/A	0	11.3	1.49	0.74	1.98
Turkey ^[37]	100	Healthy	79	N/A	N/A	N/A	N/A	N/A	21	N/A	N/A	N/A
Turkey ^[36]	92	Breast cancer patients	42.4	19.6	6	0.6	15.2	1.6	10.3	1.1	1.6	N/A
Turkey ^[39]	200	Healthy	32	35	26	N/A	N/A	6	1	N/A	N/A	N/A
Turkey ^[30]	251	Migraine patients	81.9	N/A	N/A	N/A	N/A	0.4	17.7	N/A	0	N/A
Emirates ^[23]	50+101	Healthy + antidepressants	39.1	12.2	3.3	2.5	15.2	N/A	9	N/A	N/A	4.3
Syria ^[29]	51	Healthy	47.07	30.39	2.94	0	N/A	0	9.8	0.98	0.98	3.92
Jordan ^[28]	192	Healthy	50.6	N/A	14.8	8.3	N/A	N/A	12.8	N/A	N/A	13.5

*Related to the *3, *4, and *5 together. ALL=Acute lymphoid leukemia; AML=Acute myeloid leukemia; FMF=Familial Mediterranean fever; SLE=Systemic lupus erythematosus; N/A=Not applicable

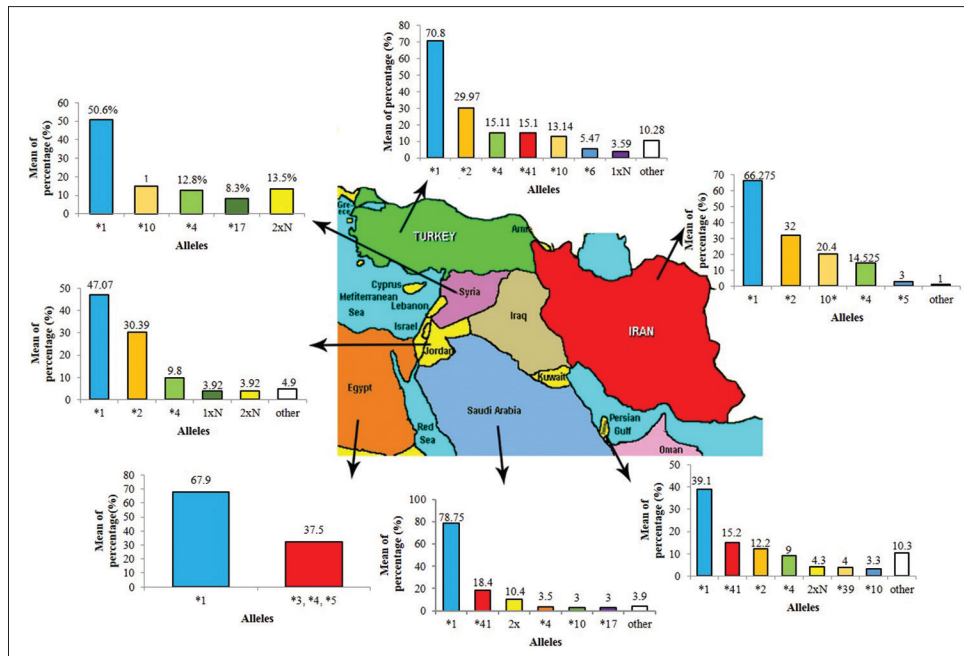


Figure 1: The allelic frequency of different cytochrome P450 2D6 alleles in the Middle Eastern countries. The frequency of the alleles with <3% accumulated in the other part of each chart. For each allele in each country, the results of studies that examined the relevant allele have been reported in the mean

distinguished from one another through the examination of the missense mutation of rs1135840 (4180G>C) for *2 assignment, and 2D6*1 could be assigned if no variants encountered. In the Middle Eastern population studied here, the frequency of CYP2D6*2 was evaluated in different studies in Iran, UAE,^[23] and Syria^[29] with the frequency of 32%, 12.2%, and 30.39%, respectively, and average frequency of 29.7% in three studies in Turkey.^[36,39,40] In these studies, apart from the CYP2D6*1 allele, the CYP2D6*2 was the most abundant allele in the population, except for the UAE,^[23] in which the frequency of CYP2D6*41 was reported to be more than CYP2D6*2. Furthermore, in the UAE,^[23] other normal alleles such as CYP2D6*27, *34, *35, *39, *43, and *46 were also examined with the frequency of 0.7%, 1%, 2%, 4%, 0.3%, and 0.3%, respectively. For all of the populations reviewed here, CYP2D6*1 allele frequency was calculated accordingly as shown in Table 1.

Of the reduced functional alleles, the CYP2D6*41 was presented in Saudi Arabia,^[13] UAE,^[23] and Turkey^[32,36] with the frequency of 18.4%, 15.2%, and 15.1%, respectively. In these populations, the CYP2D6*41 had the highest frequency between the reduced functional alleles. In terms of CYP2D6*10 allele frequency, Iran^[24,25] had the highest rate (20.4%), followed by Jordan^[28] and Turkey^[36,39,40,45] with 14.8% and 13.14% frequency, respectively. Finally, UAE,^[23] Saudi Arabia,^[14] and Syria^[29] with the frequency of 3.3%, 3%, and 2.94%, respectively, ranked the last. The CYP2D6*29 allelic frequency had only been reported in the populations of Saudi Arabia^[13] and the UEA,^[23] with a frequency of 2.9% and 1.6%, respectively. The CYP2D6*17 allele was absent in the population of Iran^[25] and Syria,^[29] but

this allele was reported with a frequency of 3%, 2.5%, and 0.85% in Saudi Arabia,^[14] UAE,^[23] and Turkey,^[36,40] with the highest frequency being in the Jordan^[28] population (8.3%). In addition, the presence of the CYP2D6*9 was reported only in the two Turkish populations^[32,40] at a frequency of 2.31%.

Of nonfunctional alleles, a low frequency of CYP2D6*7 was only observed in Turkey,^[36,40] CYP2D6*14 in Saudi Arabia,^[13] and CYP2D6*3 in Iran^[26] and Turkey.^[33,34,42-45] Furthermore, CYP2D6*5 and CYP2D6*6 showed the highest frequency in the Iranian^[25] and Turkish^[30,36,40,43,45] populations, respectively. The CYP2D6*4 allele had the highest frequency of 28.05% in Egypt^[18-21] and the lowest frequency of 3.5% in Saudi Arabia^[14] (3.5%). Between these two intervals, Turkey, Iran, Jordan, Syria, and UAE had the CYP2D6*4 abundance of 15.1%, 14.5%, 12.8%, 9.8%, and 9%, respectively. In Egypt, although some studies^[18-21] showed only the frequency of *4 among nonfunctional alleles, three studies^[15-17] reported the frequency of *3, *4, and *5 together. We averaged all of them for reporting nonfunctional alleles in the Egyptian population [Figure 1].

Among the countries that gene duplication had been studied, Turkey^[40] showed the least frequent and Saudi Arabia^[14] indicated the highest.

VARIABILITY OF THE CYTOCHROME P450 2D6 PHENOTYPE FREQUENCIES PREDICTED FROM GENOTYPES IN THE MIDDLE EAST

EM (individuals with at least one functional allele), IM (individuals with a combination of two decreased

function variants or a combination of one nonfunctional allele with a functional or reduced function variants), PM (individuals with two nonfunctional variants), and UM (individuals with more than two functional alleles) phenotype frequencies were evaluated in a study by Ingelman-Sundberg *et al.*^[48] Summary of the CYP2D6 phenotype frequencies in each country is shown in Figure 2.

Differentiating by ethnic groups, the EM frequency is found to be higher in Saudi Arabia than other countries. It is of note that Egyptian showed the highest PM and IM frequency among Middle East populations. Furthermore, UM frequency varies widely among different populations of the Middle East, with the highest frequency in Saudi Arabians.

DISCUSSION

In a previously reviewed study^[49] of the CYP2D6 allele frequencies worldwide, the Middle East was mentioned as a single area, but different countries in the Middle East were not evaluated separately. Interestingly, the result of our study in the Middle East as a whole was different from the previous one in some of CYP2D6 allele frequencies. Two of the most frequent alleles in the present study, CYP2D6*4 and *10, had been reported with less frequency in the previous study. These differences may be because limited parts of the Middle East were evaluated in the previous study, not including all the countries. Other allele frequencies were approximately the same in the two studies.

Frequency of CYP2D6 alleles in various regions of the Middle East is different. These different results are due to the different ethnic groups and different methods used. Of note, most of the articles studied here used polymerase chain reaction (PCR) restriction fragment length polymorphism (PCR-RFLP) method for determining the CYP2D6 alleles, and other methods such as real-time PCR, allele-specific PCR, and sequencing were used less. Hence, ethnic

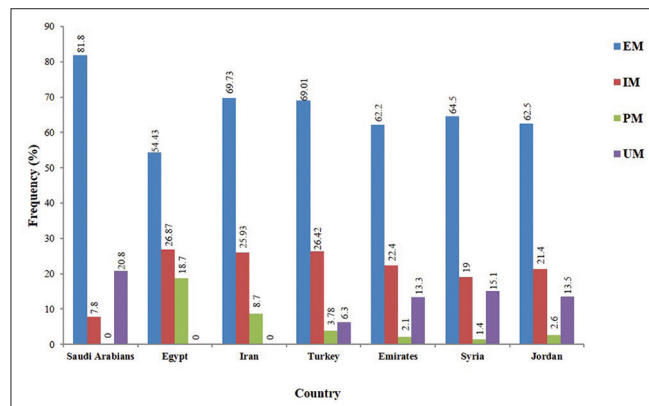


Figure 2: The genotype frequency of cytochrome P450 2D6 in different Middle Eastern countries. EM; IM; PM; and UM; frequencies was presented in the chart for each country, separately. EM = Extensive metabolizer; IM = Intermediate metabolizer; PM = Poor metabolizer; and UM = Ultrarapid metabolizer

differences seem to be more important in presenting different allelic frequencies than the discrepancy of the methods used.

Here, the comparison of the frequency of different CYP2D6 alleles in the Middle East with Asia, Africa, America, and Europe had been discussed. The incidence of CYP2D6*2 allele in the Middle East appeared to be as frequent as that in Americans (23.48%), Europeans (26.91%), and South/Central Asians (31.90%),^[10] whereas lower frequencies of this allele were reported among Africans (17.13%) and Asians (12.82%).^[9]

The allelic frequency of CYP2D6*10 in the Middle East was higher than Africans (5.47%), Americans (3.37%), and Europeans (3.16%), but much lower than those reported for Asians (42.31%). Unlike Asia, the prevalence of IM alleles mostly contributed to CYP2D6*41 (15.95%). There were no published studies on the prevalence of this allele in the Iranian ethnic populations. The CYP2D6*41 allele frequency in the Middle East was higher than that found in the Africans (10.18%), Europeans (8.56%), South/Central Asians (10.5%), Americans (5.93%), and Asians (1.97%). In addition, the CYP2D6*17 allele frequency was higher than that reported in the Europeans (0.32%) and South/Central Asians (0.38%), but much lower than Africans (19.1%). Furthermore, the allelic frequency of CYP2D6*9 in our study was comparable with Americans (1.32%) and South/Central Asians (1.4%), but lower than Europeans (2.4%) and higher than Africans (0.3%) and Asians (0.07%).^[9]

The allelic frequency of CYP2D6*3 in the Middle East was higher than that reported for Africans (0.17%) and Americans (0.73%), but was comparable with that found in the Europeans (1.2%). The allelic frequency of CYP2D6*4 in our samples was higher than that reported for Africans (4.8%), Asians (0.4%), Americans (11.3%), and South/Central Asians (6.6%), but was lower than those reported for Europeans (18.5%). Few studies had been conducted on the frequency of the CYP2D6*6 allele; nonetheless, the frequencies of this allele in Africans, Americans, Asians, and Europeans were reported to be 0.24%, 0.43%, 0.02% and 0.95%, respectively. The allelic frequency of CYP2D6*5 was comparable to Americans (1.9%), but lower than Africans (6.11%), Asians (5.61%), Europeans (2.69%), and South/Central Asians (2.54%). Our allelic frequency of CYP2D6*5 was higher than that reported in Europeans (0.11%). The *14 allelic frequency in our study was lower than Africans (0.26%), Americans (0.33%), Asians (5.61%), Europeans (2.69%), and South/Central Asians (2.54%).^[9]

CONCLUSION

Taken together, our study on the allelic frequency of CYP2D6 in the Middle East demonstrated that allele *4 is the

most frequent PM allele in this region as well as other parts of the world. In case of IM alleles, the allele *41 is the most common allele in the populations, of which the *41 allele frequency was evaluated. However, in other populations, like the rest of the world, the most abundant allele is *10. Observing the different allelic frequencies of CYP2D6 gene in this region, these results should be considered in the application of the treatment protocol.

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Conflicts of interest

There are no conflicts of interest.

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