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ORIGINAL ARTICLE

Association between Cytochrome P450 2C19 Gene Polymorphisms and Hematological Malignancies in an Iranian Population

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ABSTRACT

Background: Cytochrome P450 2C19 (CYP2C19) is widely involved in the metabolism of some medications. On the other hand, recent studies have shown the contribution of the CYP2C19 polymorphisms to different malignancies. We aimed to investigate the association between CYP2C19 polymorphism and occurrence of hematological malignancies by comparing the phenotype distribution of this enzyme in patients and healthy subjects.
Methods: 150 Iranian patients with hematological malignancies from different ethnicities were recruited. Mutant alleles of the CYP2C19*2 and *3 were examined using PCR-RFLP technique and CYP2C19*17 was genotyped using DNA sequencing analysis.
Results: CYP2C19*17 was the most common allelic variation (24%, 95% CI: 19.17-28.83%) among patients with hematological malignancies, whereas the variant CYP2C19*3 was not detected among our patients. Furthermore, the CYP2C19*1*1 and CYP2C19*1*17 genotypes which respectively represented the "extensive metabolizer" (EM) and Ultra-rapid metabolizer (URM) phenotypes, had the highest incidence.
Conclusion: The results of this study suggested that there may be no association between CYP2C19 polymorphisms and occurrence of hematological malignancies. However, larger well-designed studies are necessary to confirm these results in Iranian populations.

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Introduction

Several factors have been identified to date that have a role in the development of cancers. They include, but are not limited to environmental carcinogens and lifestyle variables. However, these factors do not affect the entire population similarly. Therefore, substantial inter-individual variability in cancer development is observed with similar exposure profiles. Beside various factors which contribute to individual susceptibility to cancer development, the role of genetic polymorphism of hepatic enzymes has also been proposed. The superfamily of cytochrome P450 enzymes is responsible for the metabolism of xenobiotics such as drugs and toxic chemicals. The carcinogenic effects of xenobiotics may either increase or decrease under the influence of cytochrome enzymes. Polymorphisms in genes encoding the liver enzymes are associated with altered enzyme function and subsequent alteration in the carcinogenecity of toxic chemicals. In order to clarify their role in cancer development, various isoenzymes of this superfamily have been explored including CYP2C19 and CYP2D6 and their impact to some types of cancers have been revealed.[1]

CYP2C19, known as the second major CYP enzyme is widely involved in the metabolism of various

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medications.[2,3] Based on published studies to date, more than 35 allele variants have been identified for CYP2C19.[4] The extent of drug and xenobiotic metabolism could be affected dramatically by these allelic variants. Compared to CYP2C19*1, as the wild type allele with normal enzymatic function, the CYP2C19*2 and CYP2C19*3 are known as defective alleles associated with poor metabolism. On the contrary, the novel variant of CYP2C19*17 is characterized by enhanced enzymatic function resulting from increased enzyme transcription.[5,6]

Previous studies have indicated significant differences in the distribution of CYP2C19*17 allele among Polish and Korean population which were 28.2% and 0.3%, respectively.[7,8] Other studies demonstrated remarkable differences in the distribution of CYP2C19*2 and CYP2C19*3 alleles in Korean and Turkish populations which were 28.4% *vs*. 10% for CYP2C19*2 and 10.1% *vs*. 0.0% for CYP2C19*3, respectively.[9,10]

There is growing evidence that reveals the association between CYP2C19 polymorphism and occurrence of different types of cancer including those of esophagus, colorectum, stomach, biliary tract, and lung. This could be explained by the major role of CYP2C19 in detoxification of carcinogens and bioactivation of procarcinogenic compounds.[11,12]

We aimed to investigate the distribution of the CYP2C19 polymorphisms in Iranian patients with hematological malignancies and explore its association with the occurrence of underlying cancer.

Materials and Methods

Patient Description and Ethical Statement

One hundred and fifty Iranian patients with hematological malignancies referring to the Shariati Hospital, Tehran University of Medical Sciences, between October 2015 and September 2016 were enrolled in the study. The mean age of participants was 37.0±15.3 years, ranging from 16 to 82 years. Written consent for the molecular study, genetic research, and publishing results was obtained from the patients. Furthermore, the Ethics Committee of Tehran University of Medical Sciences specifically approved this prospective cross-sectional study. Healthy individuals were chosen as the control group from a previously published study on the Iranian population.[13]

Genomic DNA Extraction

Genomic DNA was extracted from 5 mL of EDTA-treated whole blood samples using blood DNA kit (QIAamp® DNA Micro Kit #56304, QIAGEN, Hilden, Germany) according to the manufacturer's instruction. Purity and concentration of the extracted DNA were evaluated using Nanodrop 1000 Spectrophotometer (Nanodrop Technologies, Wilmington, DE).

Polymerase Chain Reaction (PCR) and Primer Designs

PCR was done in a final volume of 25 µL containing 100-200 ng of genomic DNA, 10 pmol of each primer (Table 1), 2.5 mM MgCl2, 200 mM of each dNTP, and 1 U of superTaq DNA polymerase (Roche Diagnostics, Mannheim, Germany). Thermocycling schedule for DNA amplification was planned as an initial denaturation at 94 ˚C for 5 min, followed by 30 cycles of denaturation at 94 °C for 1 min, annealing at 58 °C for 1 min, and elongation at 72 °C for 50 sec with a final incubation for 10 min at 72 ˚C. The oligonucleotide forward and reverse primers that were used to amplify CYP2C19 SNP were ordered as described previously.[14]

Restriction Fragment Length Polymorphism (RFLP)

The PCR products were digested with *SmaI* and *BamHI* (Fermentas, Thermo Scientific) for CYP2C19*2 (rs4244258) and CYP2C19*3 (rs4986893), respectively. Digested PCR products were analyzed using electrophoresis on a 3% agarose gel (Bio-Rad). The *SmaI* digested the 223 bp fragment to 110 bp and 113 bp fragments in wild type carrying CYP2C19*1. Digestion by *BamHI* led to the production of 142 bp and 114 bp fragments in wild type carrying CYP2C19*1. Separation of a single band through gel electrophoresis represents homozygous genotype of CYP2C19*2 and *3 (Table 1; Figure 1).

DNA Sequencing Analysis

Genotyping of the CYP2C19*17 allele was performed using DNA sequencing analysis (Figure 2), but genotyping of the CYP2C19*2 and CYP2C19*3 alleles were carried out using polymerase chain reaction RFLP (PCR-RFLP). The PCR products were sequenced using an ABI 3700 sequencer machine (Kosar Company, Tehran, Iran). All

Table 1: Details of the associated primer sequences, PCR product size, restriction endonucleases, and digested fragments of PCR products

CYP2C19 SNP	Primer sequence (14)	PCR product size (bp)	Restriction endonuclease, Temperature (°C)	Restriction pattern (bp)	Accession
CYP2C19*2 rs4244258	CAACCAGAGCTTGGCATATTG (F) TAAAGTCCCGAGGGTTGTTG (R)	223	*SmaI* (30)	Wt: 113-110 Mt: 223 Het: 223-110-113	NM_000769.2:c.681G>A
CYP2C19*3 rs4986893	CTGCAATGTGATCTGCTCCA (F) ATTCACCCCATGGCTGTCTA (R)	256	*BamHI* (37)	Wt: 142-114 Mt: 256 Het: 142 -114-256	NM_000769.2:c.636G>A
CYP2C19*17 rs12248560	GCCTGTTTTATGAACAGGATGA (F) CACAGCTCATAGCTGGCAGA (R)	215	-	-	NM_000769.2:c.-806C>T

SNP: Single Nucleotide Polymorphism; bp: base pair; F: Forward primer; R: Reverse primer; Wt: Wild type; Mt: Mutant (homozygous); Het: Heterozygous mutant

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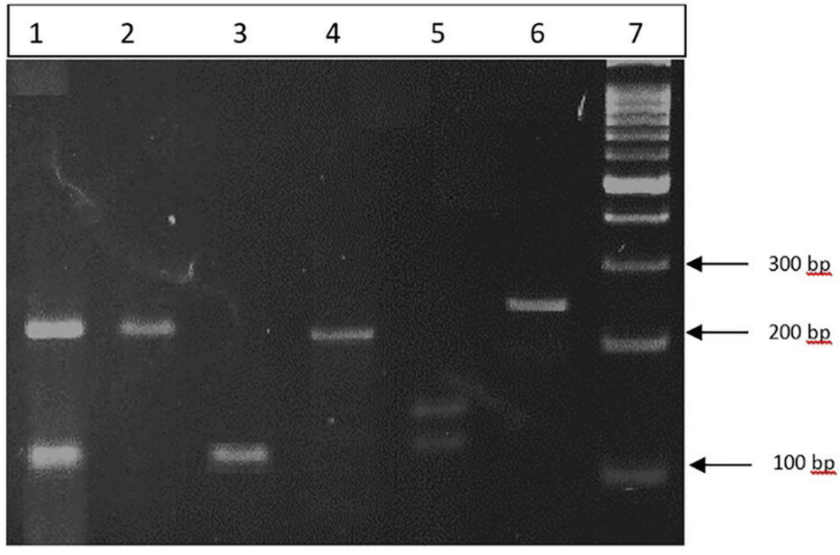


Figure 1: Sequence chromatogram of CYP2C19*17 (-806C>T) SNP

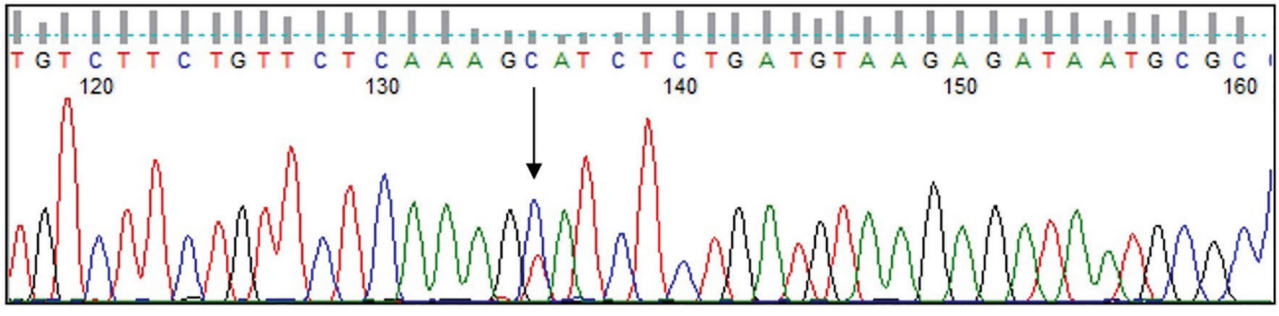


Figure 2: CYP2C19*2 Lane 1: Het mutant (223 bp, 113 bp, 110 bp), Lane 2: Mutant (223 bp), Lane 3: Wt (113 bp, 110 bp), Lane 4: PCR product (223 bp); CYP2C19*3 Lane 5: Wt (142 bp, 114 bp), Lane 6: PCR product (256 bp), Lane 7: ladder (100 bp)

fragments were then compared with controls using the FinchTV software (http://www.geospiza.com/finchtv/) and the NCBI website (available online at: http://blast.ncbi.nlm.nih.gov/Blast.cgi) for confirmation of any nucleotide variation.

Statistics

The statistical analyses were conducted using SPSS 17.0 to perform the chi-square and two-tailed Fisher's exact tests for comparison of the genotype and allele frequencies between patients with hematological malignancies and unrelated healthy individuals in an Iranian population of different ethnicities.

Confidence intervals were stated at the 95% confidence level for genotype and allele frequencies. A P value of less than 0.05 (P<0.05) was considered statistically significant.

Results

One hundred and fifty patients with hematological malignancy including 87 men and 63 women were recruited in this study. The underlying hematological malignancies consisted of AML (n:113), ALL (n:23), CML (n:6), NHL (n:4), CLL (n:2), HD (n:1), and one patient with multiple myeloma. The participants were examined to identify the allelic and genotypic distribution of CYP2C19. The CYP2C19*17 was the most common allelic variation (24.0%; 95% CI: 19.17-28.83%), whereas CYP2C19*3 was not detected among patients. CYP2C19*1*1 genotype, representing the Extensive Metabolizer (EM) phenotype, indicated the highest incidence. CYP2C19*1*17 and CYP2C19*17*17 which are associated with Ultra-rapid Metabolizer (URM) phenotype were detected in 37.3% of patients. Genotypes corresponding for Intermediate Metabolizer (IM) phenotype, which includes CYP2C19*2*17 and CYP2C19*1*2 were observed in 27.3% of the patients. The Poor Metabolizer (PM) phenotype, carrying the CYP2C19*2*2 genotype was identified in only one patient. The allelic and genotypic frequencies are summarized in Table 2.

Results of our study were compared with those previously reported for healthy individuals in Iranian population.[13] There were no significant differences in the distribution of CYP2C19*1 (61.7% *vs.* 65.3%; P=0.39), CYP2C19*2 (14.3% vs. 13.0%; P=0.56), CYP2C19*3 (0.0% vs. 0.0%; P=0.99), and CYP2C19*17 (24.0% *vs.* 21.7%; P=0.48) alleles between the two groups of patients with hematologic malignancy and normal control. Additionally, there were no significant differences in the distribution of CYP2C19*17*17 (6.0% *vs.* 5.5%; P=0.76), CYP2C19*1*17 (31.3% *vs.* 28.9%; P=0.62), CYP2C19*1*1 (34.7% *vs.* 41.7%; P=0.19), CYP2C19*2*17 (4.7% *vs.* 3.3%; P=0.53), CYP2C19*1*2 (22.7% *vs.* 18.3%; P=0.33), and CYP2C19*2*2 (0.7% *vs.* 2.2%; P=0.24) genotypes between the patients and healthy population.

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Table 2: Genotype and allele frequency of CYP2C19 among Iranian patients with hematologic malignancies (n=150). Genotype combinations were used to categorize CYP2C19 phenotypes as PM, IM, and EM

CYP2C19 Genotype	Number of subjects		Frequency; % (95% CI)	Predicted phenotype
	Men	Women		
1*1	28	24	34.67 (27.05-42.29)	EM
1*17	28	19	31.33 (23.9-38.75)	URM
1*2	22	12	22.67 (15.96-29.37)	IM
2*17	2	5	4.67 (1.29-8.04)	IM
17*17	6	3	6.00 (2.20-9.80)	URM
2*2	1	0	0.67 (0.63-1.97)	PM
3*3	0	0	0.00	PM
Alleles	Number of alleles		Frequency; % (95% CI)	
CYP2C19*1	185		61.67 (56.17-67.17)	
CYP2C19*17	72		24.0 (19.17-28.83)	
CYP2C19*2	43		14.33 (10.36-18.29)	
CYP2C19*3	0		0	

CI: Confidence Interval; EM: Extensive Metabolizer; IM: Intermediate Metabolizer; URM: Ultra-Rapid Metabolizer; PM: Poor Metabolizer

Discussion

To the best of our knowledge, this is the first study revealing the allelic and genotypic frequencies of CYP2C19*2,*3 and *17 among Iranian patients with hematological malignancies. The allelic frequencies of CYP2C19*1, *2, *3, and *17 in our study were in parallel with the previous study on healthy Iranian adults. Well-matched results were also observed for genotype frequencies.[13] Iran is a multi-ethnic country with different ethnic groups and this diversity was reflected in our patients who were recruited from ten different ethnicities. Payan and colleagues[13] included participants from only four cities which could not properly reflect the multi-ethnic nature of the Iranian population. Therefore, we further compared our findings with the results of two other studies conducted on healthy individuals from Baluch and Mazani Iranian ethnicities (Table 3).[15,16] In another study allelic and genotypic frequencies of CYP2C19*1, *2, and *3 were examined on healthy participants of Baluch ethnicity.[15] Frequency of CYP2C19*2 and *3 were in line with previous results reported by Payan et al., whereas frequencies for CYP2C19*1 allele and CYP2C19*1*1 genotype were significantly different from their findings (P=0.001) (Table 3). It should be noted that the allele frequency of CYP2C19*17 was not investigated in Ghiyas Tabari et al.[15] study, therefore this allele was identified as CYP2C19*1. If the frequency of CYP2C19*17 (21.7%) reported by Payan et al. be subtracted from CYP2C19*1 frequency (88.9%) in Ghiyas Tabari's study, the resulting values for CYP2C19*1 frequency will be close to each other (67.2% *vs.* 61.3%). Similar frequencies for CYP2C19*1*1 genotype would also be obtained accordingly. Since CYP2C19*1*17 and CYP2C19*17*17 allels were recognized as CYP2C19*1*1 in Ghiyas Tabari's study, the actual frequency of CYP2C19*1*1 would be obtained by subtracting the frequencies of CYP2C19*1*17 (28.9%) and CYP2C19*17*17 (5.5%) genotypes of Payan et al. study from CYP2C19*1*1 (78.6%) frequency reported by Ghiyas Tabari et al. study (44.2% vs. 41.2%). Since CYP2C19*17 was not investigated in Mazani population, the difference in CYP2C19*1 and CYP2C19*1*1

Table 3: Comparison of CYP2C19 allele and genotype frequencies between current and previous published studies

Study	Population (Setting)	Sample size	CYP2C19 allele frequency (%) (significant P values)				CYP2C19 genotype frequency (%) (significant P values)									
			*1	*2	*3	*17	17*17	1*17	1*1	2*17	3*17	1*2	1*3	2*2	3*3	2*3
Current study	Hemato-logical ma-lignancy	150	61.67	14.33	0	24	6	31.33	34.67	4.67	0	22.67	0	0.67	0	0
Ghiyas Tabari, et al. (2015) (15)	Baluch (unrelated healthy)	140	88.93 (P =0.001)	10	1.07 (P =0.04)	NR	NR	NR	78.57 (P =0.001)	NR	NR	20.0	0.71	0	0.71	0
Hashemi-Soteh et al. (2013) (16)	Mazani (unrelated healthy)	103	91 (P =0.001)	9	0	NR	NR	NR	84 (P =0.001)	NR	NR	14	0	2	0	0
Payan et al. (2015) (13)	Four cities (unrelated healthy)	180	65.3	13	0	21.7	5.5	28.9	41.7	3.3)	0	18.3	0	2.2	0	0

Only significant p-values are stated in the table.

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frequencies of Payan et al. study with this population could be justified in the same way.[16] Therefore, it could be claimed that the distribution of CYP2C19 polymorphism in our study was not significantly different from those reported in previous studies.

Regardless of the ethnolinguistic diversity of the Iranian population, Farjadian and colleagues conducted a study on different Iranian ethnicities and demonstrated that all Iranian ethnicities are branched from the same origin which is in close proximity to the eastern Mediterranean region.[17] Considering the similar distribution of CYP2C19 polymorphisms obtained from the aforementioned studies, and the findings of the mentioned study, it could be claimed that the main findings of our study were not confounded by ethnic diversity in the Iranian population.

In reviewing the literature, there was a significant association between CYP2C19 polymorphism and incidence of some cancers. A remarkable association between PM phenotype of CYP2C19 and risk of digestive tract cancers was demonstrated in a meta-analysis by Zhou and colleagues.[12] This association could be justified by the role of CYP2C19 in detoxification of carcinogens and activation of procarcinogenic agents.[12] Sameer and colleagues conducted a study on 52 children with hematological malignancies in the Gaza strip and distribution of the CYP2C19 polymorphisms were determined and compared with 200 healthy subjects. Their findings showed that there was no significant association between CYP2C19 polymorphism and the occurrence of hematological malignancies.[18] With respect to long-term exposure of adults to environmental carcinogenic and procarcinogenic compounds, such association remains a matter of debate in adults.

The allelic and genotypic distribution of CYP2C19 were similar between our study population and the control group of healthy Iranian subjects. These findings are consistent with those of Sameer et al. which found no association between CYP2C19 polymorphism and the occurrence of hematological malignancies in children.[18] Although preliminary, it could be suggested that there is no association between CYP2C19 polymorphism and occurrence of hematological malignancies.

The sample size of the study was not large enough to investigate the association of CYP2C19 polymorphisms and each specific hematological malignancy.

Conclusion

The evidence from this study suggested that the distribution of CYP2C19 allelic and genotypic frequencies was not significantly different between patients with hematological malignancies and healthy individuals. Hence, we found no association between cytochrome CYP2C19 gene polymorphism and occurrence of hematological malignancies, suggesting that this polymorphism may not be a risk factor for patients with such malignancies among Iranian population of different ethnicities.

Conflict of Interest: None declared.

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