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Evaluation of G2677T/A polymorphism of *MDR1* gene by polymerase chain reaction in Mazandaran province, Iran

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Abstract

The human *MDR1* gene encodes for a P-glycoprotein (PGP), which acts as an efflux pump that transports a large variety of substrates from the inside of cells to the outside until protection against xenobiotics. The G2677T/A polymorphism in exon 21 is associated with PGP expression and function in humans. The present study was aimed to determine the frequencies of this polymorphism in a healthy population from Mazandaran province of Iran. A total of 120 unrelated healthy subjects from Mazandaran province, residing in Sari, coming for blood donating at Sari Blood Transfusion Center were enrolled. Genomic DNA was extracted from the peripheral blood lymphocytes of each subject. All subjects were genotyped for G2677T/A polymorphism by polymerase chain reaction-restriction fragment length polymorphism method.

The genotype frequencies were G2677G (65%), G2677T (20.83%), G2677A (14.17%) and TT, AA, TA genotypes were not observed. Moreover, frequency of G allele (82.5%) was significantly ($p < 0.05$) higher than the T (10.42%) and A (7.08%). This is the first study to investigate the G2677T/A polymorphism of *MDR1* gene in population from Mazandaran province of Iran. These data may be relevant for dose recommendation of PGP substrate drugs and can help for individualizing drug therapy of organ transplantation and important diseases such as cancer and AIDS, congestive heart failure and etc.

Keywords: P–glycoprotein, G2677T/A polymorphism, Iranian population, *MDR1*

Introduction

ATP Binding Cassette (ABC) transporters are a family of transmembrane proteins that translocate molecules across biological membranes (1). Human Multidrug Resistance1 (*MDR1*, also referred to as ABCB1) is probably the best characterized of the ABC xenobiotic efflux transporters that is located on choromosome 7q21 (1,2). The *MDR1* gene encodes P-glycoprotein which functions as an ATP-dependent exporter of substances from inside of cells to the outside (3). PGP was first observed in tumor cells for conferring resistance against anti-cancer agents (4,5). In addition, it is expressd in normal tissues including White blood cells, liver, kidneys, small and large intestine, the biliary ducts, pancreas, placenta, brain and testis (6).

PGP is involved in the absorption, distribution and excretion of xenobiotics, numerous drugs and toxins into bile and urine (7-9). PGP can protect the organism from environmental toxins and carcinogens, it can also prevent the penetration of drugs

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into the brain, testis or fetus because of its accumulation in the blood-tissue barrier and blood-fetus barrier (10-13). PGP transports broad substrates including anti-HIV drugs, cardiac glycosides, steroids, several anticancer drugs, antibiotics, immunosuppressants and drugs in other categories (14).

Recently several single nucleotide polymorphisms (SNPs) have been reported in the *MDR1* gene (15). Polymorphisms in this gene can affect the metabolism of drugs, the pharmacological action and toxicity profile of a vast number of therapeutic agents (16,17). The first mutations in *MDR1* gene in normal cells were G2677T/A, C3435T and G2995A that were defined by Mickley (18). Among them, G2677T/A was the most extensively evaluated in relation to PGP expression. G2677T/A is a non-synonymous SNP, which is located at exon 21 in the second transmembrane domain. G2677T mutation leading to the substitution of Serine in place of the usual Alanine at amino acid 893 and G2677A mutation leading to amino acid exchange from Alanine to Threonine (13). G2677T/A polymorphism has impact on the expression and activity of PGP and alters in vivo drug disposition and drug effects (19-21).

So far, significant interethnic differences in allele and genotype frequencies of C3435T and other *MDR1* SNPs have been reported. Considering the well-known influence of *MDR1* on the bioavailability and pharmacokinetics of various drugs, genotyping of *MDR1* polymorphisms and determination of haplotypes may become an important tool for predicting individual susceptibility to development of drug resistance (15). In this investigation, allele and genotype frequencies of the G2677T/A *MDR1* gene was determined in a population from Mazandaran province (Sari, Iran) to obtain data relevant for this ethnic group.

Materials and methods
Study population
The present study included 120 randomly selected (110 men and 10 women; mean age 35.78 ± 10.08), healthy, unrelated individuals from Mazandaran province, residing in Sari, coming for blood donating at Sari Blood Transfusion Center during the period of May 2012– July 2012 fulfilling our inclusion and exclusion criteria. Individuals were eligible for study if they had no history of any chronic diseases or cancers and were enrolled after a written informed consent was obtained. Ethnicity was recorded by self-report. The protocol of the study was approved by the research ethics committee of Mazandaran University of Medical Sciences.

PCR Amplification
DNA was isolated from whole blood samples using a DNG^{TM} plus Kit (Cinnagene, Iran) according to the manufacture's protocol. G2677T/A polymorphism was detected based on Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The PCR primers for G2677T/A polymorphism in exon 21 were:

Forward : 5'-TACCCATCATTGCAATAGCAG-3'
Reverse (G2677G) : 5'-TTTAGTTTGACTCACCTTGCTAG-3'
Reverse (G2677T) : 5'-TTTAGTTTGACTCACCTTTCTAG-3'
Reverse (G2677A) : 5'-TTTAGTTTGACTCACCTTCCC-3'

The PCRs were performed in a 30 μL reaction volume containing 2 μL of DNA, 0.2 mM of each dNTP , 1.5 mM MgCl$_2$, 1U Taq DNA polymerase, 3 μL of 10x PCR Buffer, 1μL of each forward and reverse primers and 21 μL water.

The PCR protocol was as follows: initial 5 min at 94 °C followed by 38 cycles, consisting of denaturation for 40s at 94 °C,

annealing for 40s at 60 °C to 62 °C, and extension for 40s at 72 °C and terminal elongation was performed for 5min at 72 °C. Amplified segments electrophoresed on 1% agarose gel containing 5 µg/ml ethidium bromide (22) .

Detection of G2677T/A polymorphism
The genotype frequencies for each SNP in the study were determined by the RFLP method. The GenBank accession number of MDR1 reference used in this study is M14758. The PCR product (107 bp) was digested at 37 °C for 16 h with 2 U of NheI restriction enzyme for G2677G, 2 U of XbaI restriction enzyme for G2677T and 2 U of AfaI restriction enzyme for G2677A (22). The restriction digested products were analyzed by electrophoresis on 3% agarose gel containing ethidium bromide and visualized under UV illumination.
Digestion fragments for G2677T/A polymorphism are shown in Table 1

Sequencing
DNA sequencing method was carried out for several PCR product.

Statistical analysis
Genotype and allele frequencies between groups were analyzed using SPSS version 18 included the chi-square test (χ^2). A p-value of less than 0.05 was considered

statistically significant. Ninety-five percent confidence intervals were calculated for all observed allele and genotype frequencies. Allele and genotype frequencies for SNPs were assessed for deviation from the Hardy-Weinberg equilibrium.

Results
Demographics of the study groups
We analyzed samples obtained from 120 healthy unrelated individuals to detect G2677T/A polymorphism of the *MDR1* gene in 2677 position.

Allele frequency and genotype distribution
Fig.1 illustrates the results of the genotypes by their PCR product length. The allele and genotype frequencies of *MDR1* variants in 2677 position are given in Table 2. Eight PCR products spanning *MDR1* G2677T/A were sequenced and the results were consistent with those determined by the PCR. Results for two representative samples carrying 2677 GG and GT are shown in Fig.2.
In our study, the frequencies of the G, T and A alleles was obtained 82.5%,

Table 1 Digestion fragments for G2677T/A polymorphism (22)

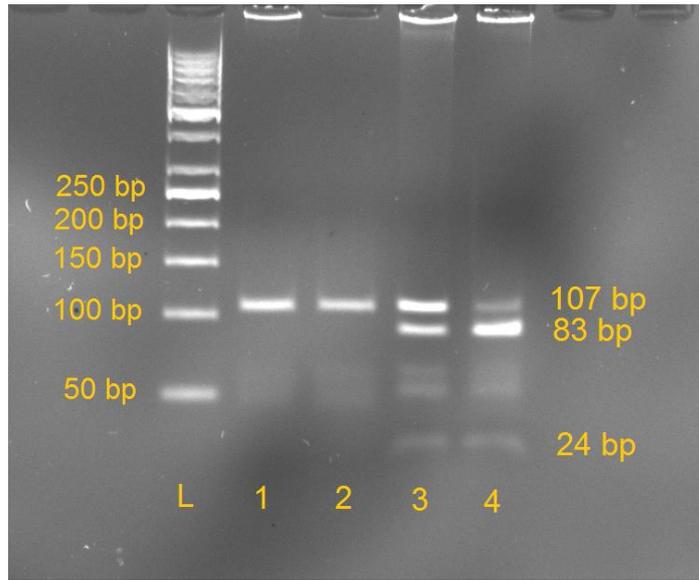|	Length (bp)	Restriction Enzyme	Cutting Position	Wild/Wild	Wild/Mutant	Mutant/Mutant
G2677G	107	NheI	83	24,83	24,83,107	107
G2677T	107	XbaI	83	107	24,83,107	24,83
G2677A	107	AfaI	83	107	24,83,107	24,83

Figure 1 Results of PCR-RFLP analysis of MDR1 G2677T/A SNP.L: 50 bp DNA ladder ; Lane 1: PCR product (107 bp) ; Lane 2 : GG genotype ; Lane 3 : GT genotype ; Lane 4 : GA genotype.
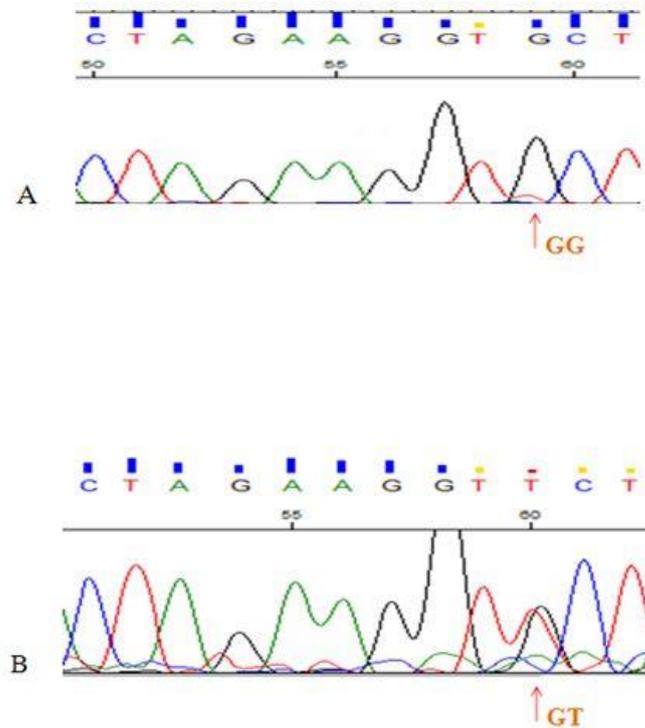

Figure 2 DNA sequences of MDR1 G2677T/A single nucleotide polymorphism. A : GG genotype , B GT genotype.

Table 2 The allele and genotype distributions of *MDR1* G2677T/A in Mazandaran province (Sari)

	Frequency (%)	95%CI
MDR1 G2677T/A genotype*		
GG	78 (65)	73.53 – 56.46
GT	25 (20.83)	28.09 – 13.56
GA	17 (14.17)	20.40 – 7.93
MDR1 G2677T/A allele*		
G	198 (82.5)	87.30 – 77.69
T	25 (10.42)	14.28 – 6.55
A	17 (7.08)	10.32 – 3.83

*P < 0.05.
CI: confidence interval.

10.42% and 7.08% respectively (P < 0.05). GG, GT and GA genotype frequencies were 65, 20.83 and 14.17% respectively (P < 0.05) and TT, AA, TA genotypes were not observed. The observed genotype frequencies did not deviate significantly from those expected at Hardy-Weinberg equilibrium.

We found that frequencies of *MDR1* G allele in our population is significantly higher than that the usual rate in Asian (23-26), Caucasian (15,27-32) and American (33) populations, but the frequencies of *MDR1* T allele is significantly lower than all studied-populations. Moreover, frequencies of *MDR1* A allele in our population is similar to Indian (26), higher than Caucasian (15, 27-32) and American (33) populations, lower than Chinese (25), Japanese (24) and Korean (23) populations. We have shown the allele and genotype frequencies of the G2677T/A polymorphism in

Mazandaran province (our study) and other populations in Table 3 and Table 4.

Discussion
Genetic polymorphisms have important effects on the response of a patient to drug therapy, on drug metabolizing enzymes and on the target of drugs (34-37). Expression of PGP, the product of the *MDR1* gene, is an important factor influencing the bioavailability of many cardiovascular and anticancer medications with a narrow therapeutic window. Because *MDR1* polymorphisms have an impact on the pharmacokinetic and pharmacodynamic profiles of drug substrates and directly influence the outcome and prognosis of certain diseases, it is clear that *MDR1* polymorphism analysis can provide important information to optimize the individualized therapeutic approach (15). The Present study investigated the frequency of a commonly known *MDR1*

Table 3 Comparison of allele frequencies of MDR1 G2677T/A polymorphism reported for Iranian population with other populations published.

	Population	Allele frequency				Reference
		n	G	T	A	
Asian	Iranian (Mazandaran province)	120	0.825	0.104	0.070	This study
	Indian	87	0.333	0.598	0.069	(26)
	Chinese	200	0.417	0.450	0.133	(25)
	Japanese	154	0.428	0.406	0.166	(24)
	Korean	632	0.438	0.391	0.171	(23)
Caucasion	British	285	0.579	0.396	0.025	(32)
	Polish	204	0.595	0.385	0.020	(31)
	Serbian	158	0.530	0.430	0.040	(15)
	Czech	189	0.539	0.458	0.003	(30)
	Bulgarian	160	0.559	0.441	N.A	(29)
	Scottish	370	0.512	0.498	N.A	(28)
	Slovenian	355	0.600	0.400	N.A	(27)
American	Brazil	106	0.610	0.380	0.010	(33)

G: wild- G: G: wild-type allele, T,A: mutant allele, n: number of subjects.

genetic polymorphism, G2677T/A, in a sample of Iranian population (Mazandaran province, Sari). As indicated in Table 3, the GG genotype frequency in our population was found 82.5% that is higher than Asian, Caucasian and American populations. The frequency of GT genotype in our population is lower than all populations. Our results showed similarity in GA genotype with Chinese, Japanese and Korean populations and is higher than Caucasian, American and Indian populations. The frequency of 2677G allele is the lowest in India and is the highest in Brazil, Slovenia, Polish and our population.

In a study, Mcdonald and colleagues discussed the role of PGP in limiting brain absorption of ivermectin pesticides. They expressed 2677T is the prevalent non-synonymous human SNP, while 2677A occurs at a much lower allelic frequency (2).

As it is seen in Table 4, the frequency of 2677A allele is the lowest in Czech and it is seen mostly in Asian countries. The frequency of 2677T allele is the lowest in our population and is the highest in India. Potocnik and colleagues have evidenced that a higher frequency of T allele in position 2677 of *MDR1* was indicated in patients with colorectal cancer when compared with healthy subjects (38). They showed that G2677T/A polymorphism correlated with altered expression of PGP and activity in colon tissue. In another study,

Table 4 Comparison of genotype frequencies of MDR1 G2677T/A polymorphism reported for Iranian population with other populations published.

Population		n	GG	GT	TT	GA	AA	TA	Reference
						Genotype frequency			
Asian	Iranian (Mazandaran province)	120	0.65	0.208	0	0.141	0	0	This study
	Indian	87	0.138	0.310	0.414	0.081	N.d	0.58	[26]
	Chinese	200	0.175	0.375	0.210	0.110	0.025	0.105	[25]
	Japanese	154	0.195	0.318	0.182	0.149	0.026	0.130	[24]
	Korean	632	0.191	0.339	0.163	0.155	0.035	0.117	[23]
Caucasion	British	285	0.329	0.474	0.147	0.025	N.d	0.025	[32]
	Polish	204	0.387	0.397	0.176	0.020	N.d	0.020	[31]
	Serbian	158	0.26	0.52	0.15	0.03	0	0	[15]
	Czech	189	0.296	0.471	0.222	0.05	N.d	N.d	[30]
	Bulgarian	160	0.344	0.431	0.225	N.a	N.a	N.a	[29]
	Scottish	370	0.276	0.470	0.254	N.a	N.a	N.a	[28]
	Slovenian	355	0.375	0.445	0.18	N.a	N.a	N.a	[27]
America	Brazil	106	0.400	0.400	0.180	0.020	N.d	N.d	[33]

G: wild-type allele, T, A: mutant allele, n: number of subjects.
ND : not detected. NA : not analyzed.

Sapmaz and colleagues investigated the G2677T/A polymorphism in the *MDR1* gene in Turkish patients with inflammatory bowel disease and a healthy control group. They concluded that G2677T/A polymorphism was not found to be a risk factor for Crohn's disease or ulcerative colitis (39).

Penna and colleagues examined *MDR1* polymorphism G2677T in B-chronic lymphocytic leukemia in Italian Population. They observed higher T allele frequency in patients with B-CLL when compared with controls (16). Heterozygous genotype may lead to a different of the encoded protein and mRNA expression. Zhou and colleagues investigated the association between G2677T/A polymorphism and chemosensitivity of paclitaxel in Chinese advanced gastric cancer patients. They concluded that G2677T/A polymorphisms can affect the chemosensitivity of paclitaxel and responsiveness (40). Another study conducted by Ichihara and colleagues examined the association of this polymorphism of *MDR1* with obesity in Japanese individuals (41). They claim that the G2677T/A polymorphism of MDR1 was significantly associated with the prevalence of obesity. G2677T/A polymorphism may be related with deep changes in the levels of hormones or other physiological molecules.

In conclusion, our study established the frequency of *MDR1* G2677T/A polymorphism in the population from Mazandaran province of Iran. Considering the number and significance of PGP substrates, determination of the frequency of functionally important SNPs in the *MDR1* gene provides useful data for the evaluation of inter-individual differences in drug response. Moreover, these data can be used for the prediction of any adverse effects and the possibility of adverse reactions during treatment with PGP-substrate drugs in patients residing in our province. The recent identification of multiple SNPs in the *MDR1* gene and in other genes (such as *CYP3A4/5, CYP2D6, CYP2C19, NAT2* and *UGT1A1*) that are involved in drug metabolism provides an opportunity for the development of molecular tools for drug and dose modification for each patient. However, the relative importance of variability in PGP function due to exogenous and genetic factors for drug disposition, therapeutic outcome and disease risk needs to be clarified in future studies in our province.

Conflict of interest
The authors declare that there is no conflict of interest.

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