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Determination of the frequency of ABCB1 gene polymorphisms (C1236T, C3435T) in the population of the Tashkent region of Uzbekistan

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ABSTRACT

This work aimed to determine the frequency of 2 polymorphisms in the ABCB1 gene (C1236T, C3435T) in healthy volunteers from the population of Tashkent region of Uzbekistan to assess their prevalence and improve the quality of personalized therapy and treatment efficacy. The study included 121 conditionally healthy volunteers from the Tashkent region of Uzbekistan aged 18 to 54 years. Genotyping was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism. It was found that for C1236T, the T allele had a higher frequency (0.63) than the C allele (0.37). Regarding genotypes, CT and TT were found significantly more often than CC. The frequency of the C3435T C allele was 41%, and that of the T allele was 59%; the CT and TT genotypes were detected equally and had a frequency higher than that of CC. In conclusion, we observed a high frequency of altered alleles of C1236T and C3435T polymorphisms of the ABCB1 gene among healthy volunteers of the Uzbek population. Thus, such research needs to be scaled up to select the optimal individual therapy for many diseases.

Keywords: P-glycoprotein, SNP, genotype.

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INTRODUCTION

The main goal of personalized medicine is to optimize and individualize prevention and treatment, taking into account the individual characteristics of each person. Indeed, each person has a particular genetic makeup that influences the risk of developing diseases and interactions with environmental factors and determines response to drug therapy (Collins, 1991). There are more than 14 million single nucleotide polymorphisms (SNPs) in the human genome (Roden and George, 2002). Consequently, the identification of DNA variants that most significantly contribute to population changes is one of the fundamental tasks of genetics (Sachidanandam et al., 2001).

Individuals respond differently to therapy, which may explain why treatments that have been proven effective in some patients may fail to elicit adequate responses in others. In addition, a lack of response to therapy can cause serious side effects or even death, which affects individual variability in drug safety and efficacy. The causal factors for such variability are complex and multiple, with direct or indirect consequences. Among them, stably inherited genetic factors are the main variables (Pirmohamed, 2006); other variables include environmental factors, (chemicals and radiation exposure), lifestyle factors, (physical activity and bad habits) and physiological factors, (age, sex, function liver and kidney, pregnancy) (Meyer et al., 2013).

The drug response of individual patients is primarily determined by the pharmacokinetic and pharmacodynamic properties of the prescribed drugs, which are directly or indirectly affected by polymorphisms in genes that encode enzymes and transporters that

metabolize drugs, and different populations have different allele frequencies of genes for both drug-metabolizing enzymes and carriers. It is well known that individuals differ significantly in clinical response to drugs. This interindividual bias is often a problem for optimizing dosing regimens, as most drugs are effective in only 25 to 60% of patients (Wilkinson, 2005). Moreover, many patients do not benefit from the first recommended drug treatment. For example, on average, 38, 40, 43, 50 and 75% of patients with depression, asthma, diabetes, arthritis, and cancer, respectively, do not respond to initial treatment (Spear et al., 2011).

Overall, a drug can have a positive or toxic effect on a particular patient. The nature and degree of the effect obtained largely depends on the rate of absorption, distribution and excretion of the drug. Drug transporters control the movement of almost all drugs and their active or inactive metabolites into and out of cells. Therefore, polymorphisms in drug carrier genes can change the rate of absorption, distribution and excretion and, ultimately, the safety and efficacy of administered drugs.

More than 400 transporters are known to date, which is grouped into two main superfamilies — solute carriers (SLCs) and ATP-binding cassettes (ABCs) (Kotlovsky et al., 2015). Many of these transporters have been characterized at the molecular level and are present in tissues and cell membranes of the human body (International Transporter Consortium et al., 2010).

In total, 48 ABC transporters have been identified in humans; the most important representative of the ABC superfamily of transporters is P-glycoprotein (from English permeability) or ABCB1/MDR1 protein, the most studied transporter of many drugs (Brambila-Tapia, 2013; Yakusheva et al., 2014). The phenomenon of multidrug resistance (MDR) can be caused by various mechanisms, particularly a decrease in the accumulation of a drug in a cell associated with the functioning of P-glycoprotein. P-glycoprotein (Pgp) is a large transmembrane protein with a molecular weight of 170 kDa that consists of 1280 amino acids grouped into 2 homologous halves 136 A in height and 70 A in width, connected by a mobile polypeptide that ensures their conformational stability (Sharom, 2012). The gene encoding this protein maps to chromosome 7q21.1 and consists of 28 exons and 27 introns (Jose and Thomas, 2009). In 2000, Hoffmeyer and colleagues described 15 polymorphisms in the ABCB1 gene in humans (Hoffmeyer et al., 2000).

P-glycoprotein is found in many organs and tissues of humans. In the liver, it is located on the surface of hepatocytes, on the apical surface of the small biliary ducts, in the small and large intestine on the apical surface of epithelial cells, in the kidneys on the membrane of proximal tubules, and the pancreas on the apical surfaces of small ducts (Tashenova, 2010). Additionally, P-glycoprotein is found in endotheliocytes of histohaematogenous barriers (blood-brain, haemato-ovarian, haemato-testicular and haemato-placental), in cells of the immune system (mature macrophages, killer cells, T- and B-lymphocytes, monocytes), and epithelial cells (Lee et al., 2010). In the intestine, P-glycoprotein acts as a kind of pump that "pumps out" drugs from the cell into the intestinal lumen. In hepatocytes, P-glycoprotein promotes the secretion of xenobiotics into the bile. Moreover, in the epithelium of renal tubules, it is involved in the active excretion of xenobiotics into the urine. In endothelial cells of histohaematogenous barriers, P-glycoprotein prevents the penetration of xenobiotics into the central nervous system, ovaries, testes, and placenta (Tashenova, 2010).

Thus, P-glycoprotein is linked to an adaptation mechanism that arose during evolution to protect the body from xenobiotics. The main function of P-glycoprotein is to hinder the absorption of xenobiotics; when they enter the body, they are rapidly excreted (Bochanova, 2017). It should be noted that the content of P-glycoprotein is significantly different in men and women. It has been shown that expression of the gene encoding P-glycoprotein (ABCB1) is 2.4 times higher in men than in women (Bobrova et al., 2017), and it has been proposed that this phenomenon underlies sex differences in the pharmacokinetics of a number of drugs (Cummins, 2002). P-glycoprotein substrates include a number of widely used drugs: cardiac glycosides, slow calcium channel blockers, HMG-CoA reductase inhibitors (statins), H1-histamine receptor blockers, macrolides, some cytostatics, and antiretroviral drugs, among others (Kim, 2002).

The most studied and widespread of the 50 known single-nucleotide polymorphisms of the ABCB1 gene are rs1128503 (C1236T) and rs1045642 (C3435T), which are observed with a frequency of 50 to 60% in Caucasians, 40 to 50% in Asians, and 10 to 30% in Africans (Kesimci et al., 2012). Although the polymorphisms C1236T (in the 12th exon) and C3435T (in the 26th exon) do not lead to amino acid substitutions, they cause a change in gene expression.

The aim of our work was to determine the frequency of genotypes for two polymorphisms of the ABCB1 gene (C1236T and C3435T) in healthy volunteers of the population of Tashkent region of Uzbekistan to assess the prevalence and improve the quality of personalized therapy and treatment efficacy.

MATERIALS AND METHODS

This study included 121 conditionally healthy volunteers from the population of the Tashkent region of Uzbekistan aged 18 to 54 years (of whom 61 were men, 60 women). The average age of the subjects was 28.3 ± 7.5 years. This study was approved by the Ministry of Health of the Republic of Uzbekistan Ethical Committee under the number № 3/1-1023 (30 march of 2019). All participants signed informed consent. The study excluded those with severe chronic diseases of the heart system, diabetes type 1 or 2, or cancer.

Molecular genetic examination of the participants was carried out

in the genomics laboratory of the Institute of Biophysics and Biochemistry at the National University of the Republic of Uzbekistan named after I. Mirzo Ulugbek and the Center for Advanced Technologies under the Ministry of Innovative Development of the Republic of Uzbekistan. Genomic DNA was isolated from 1 ml of venous blood using a Diatom Prep100 kit (Izogen, Moscow). Genotyping was performed by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis. PCR was carried out on a Gene Amp® PCR 9700 - amplifier (Applied Biosystems, USA) using an IsogeneGenPak®PCR-Core lyophilic reagent kit. The primers presented in Table 1 were used to amplify ABCB1 gene polymorphisms C1236T and C3435T.

The length of the products after amplification was 548 bp and 558 bp, respectively. The PCR cycling was as follows: denaturation at 94°C for 5 min, 40 cycles of denaturation (94°C/25 s), annealing (55°C/35 s), and synthesis (72°C/35 s), and 72°C for 4 min. Then, seven microlitres of C1236T and C3435T PCR products were digested with restriction enzymes BsuRI and BSTBM1, respectively. The reaction products were analysed by 3% agarose gel electrophoresis with the addition of ethidium bromide and visualized using a UV emitter. In samples with genotype 1236CC, BsuRI cleaves the 558 bp PCR product into fragments of 218 bp and 295 bp. Genotype 1236TT is determined by the presence of 253 bp and 295 bp fragments. A heterozygous sample contains all 3 fragments of 218 bp, 253 bp and 295 bp. In C3435T CC genotype samples, fragments of 103 bp, 172 bp and 236 bp are obtained. For TT homozygotes, fragments 103 bp and 408 bp in length are produced. Regarding the statistical analysis of the data, the frequencies of alleles and genotypes for different alleles were estimated according to the results of the abovementioned PCR-RFLP method. The distribution of genotypes was assessed for Hardy-Weinberg equilibrium (HWE) using the χ2 test. Statistical analysis was performed using Excel for Windows and an online calculator https://www.openepi.com/. The critical level of significance was 0.05.

Table 1. Primers for specific amplification of MDR1 gene polymorphisms C1236T and C3435T.

Gen	Names of primers		Nucleotide sequence (5^{l}-3^{l})
ABCB1 (MDR1)	C1236T rs1128503	Forward	GTTCACTTCAGTTACCCATCTCG
		Revers	CGTGGTGGCAAACAATACAGG
	C3435T rs1045642	Forward	GTGTGCTGGTCCTGAAGTTG
		Revers	TGGAGCCTCAAGCCTATAGC

RESULTS

To determine the frequency of occurrence of the studied polymorphisms, genotype analysis was carried out. The distribution of genotypes is presented in Table 2. The observed distribution of genotype frequencies for the studied polymorphism corresponds to the theoretically expected Hardy-Weinberg equilibrium distribution (χ2 = 0.08, P = 0.77). The frequencies of the mutant allele for the C1236T and C3435T polymorphisms were 0.63 and 0.59, respectively.

The prevalence of the frequencies of the studied polymorphisms depending on sex was also evaluated. The parameter was statistically the same for males and females in all three genotypes (Table 3).

The simultaneous presence of ABCB1 C3435T and C1236T polymorphisms was also assessed. As shown in Table 4, the simultaneous presence of heterozygous and mutant genotypes was most common (3435 CT/1236 CT - 27%, 3435 TT/1236 TT - 21%), significantly higher than the frequency of the 3435 CC/1236 CC genotype.

Table 2. Prevalence of alleles and genotypes of ABCB1 gene polymorphisms among 121 Uzbek volunteers.

Polymorphism	Genotype frequency (n)			Allele frequency		χ^2	p
C1236T	CC 0.13 (16)	CT 0.48 (58)	TT 0.39 (47)	C – 0.37	T – 0.63	0.08	0.77
C3435T	CC 0.18 (22)	CT 0.46 (55)	TT 0.36 (44)	C – 0.41	T – 0.59	0.13	0.51

Table 3. Comparison of the frequencies of distribution of alleles and genotypes among males and females.

Polymorphism / Sex	Frequency of occurrence of C1236T. (n)					Frequency of occurrence of C3435T. (n)				
	CC	CT	TT	C	T	CC	CT	TT	C	T
Male	0.16 (10)	0.41 (25)	0.43 (26)	0.37	0.63	0.18 (11)	0.49 (30)	0.33 (20)	0.43	0.57
Female	0.1 (6)	0.55 (33)	0.35 (21)	0.37	0.63	0.18 (11)	0.42 (25)	0.4 (24)	0.39	0.61
P value	0.15	0.06	0.19	0.46		0.48	0.2	0.2	0.2	

Table 4. Frequency of simultaneous presence of genotypes of the studied ABCB1 gene polymorphisms in 121 Uzbek volunteers.

Genotypes	Number of people	Frequency
3435TT/1236CC	1	0.009
3435CC/1236TT	4	0.033
3435CC/1236CC	8	0.066
3435CT/1236CC	8	0.066
3435CC/1236CT	9	0.074
3435CT/1236TT	15	0.12
3435TT/1236CT	17	0.14
3435TT/1236TT	26	0.21
3435CT/1236CT	33	0.27

DISCUSSION

In recent years, a large amount of published data has provided interesting evidence for the effect of ABCB1 gene SNPs on Pgp function. These polymorphisms are potential factors of interindividual and interethnic variability in drug response (Sai et al., 2003; Xu et al., 2008; Rubiś et al., 2012) and susceptibility to certain diseases. In this study, we analysed the 2 most common SNPs of the ABCB1 gene, namely, C1236T and C3435T, and present the allele frequencies and genotypes in comparison with the general indicators for different populations.

One of the most common polymorphic variants of the MDR1 gene is the synonymous single-nucleotide polymorphism rs1128503 (C1236T, Gly412Gly). According to the SNP database, the C allele of the rs1128503 (1236C> T) variant has a frequency of 30 to 93%, depending on the ethnic population. At the same time, the C allele is a minor allele in Asians, whereas the T allele is a minor allele in Africans. Numerous studies have characterized potential phenotypic associations with the rs1128503 (C1236T) variant of the ABCB1 gene, and an increase in drug exposure or drug response associated with genotype 1236 CC (Schaich et al., 2009) and genotype 1236 TT (Mathijssen et al., 2003; Ofori-Asenso and Agyeman, 2016) was found. In our study, the T allele of C1236T had a higher frequency (0.63) than the C allele (0.37) (P = 0.77). The revealed frequency of the wild-type allele 1236_C in exon 12 was 37%, which slightly differs from the data obtained in European populations (52 to 58%) (Naumovska et al., 2014). In Iran, the frequency of the C allele is also high at 63.9% (Saidijam et al., 2015). Our data on the prevalence of the T allele are similar to those in Asian populations, with a frequency for the T allele in the Chinese population of 58 to 72% (Li et al., 2007; Yan et al., 2017; Ji et al., 2018) and the Indian population of 67% (Chowbay et al., 2003). In the case of genotypes, CT and TT were found significantly more often than CC.

The synonymous single-nucleotide polymorphism rs1045642 (C3435T) shows significant interethnic differences in allele frequency, with the 3435 C allele varying between 34 and 90% in different populations of the world (Schwab et al., 2003; Dey, 2006).

In the present work, the frequency of ABCB1 gene C3435T single-nucleotide variant among healthy volunteers of the population of the Tashkent region was determined. The frequency of the C allele was 41%, and that of the T allele was 59% (P = 0.51). The frequency of the 3435T allelic variant in our population is quite high and comparable with the data obtained in the Japanese population (Komoto et al., 2006); the prevalence of the mutant T allele is 52% in Germany (Cascorbi, 2006), 52.4% in Poland (Tan et al., 2004), and 54.4% in the Russian population (Gaikovitch et al., 2003). This polymorphism is associated with altered P-glycoprotein activity. The high frequency of the C allele implies overexpression of Pgp (Marie-Genica, 2010), which can affect drug absorption and bioavailability, especially in the central nervous system. Hence, this polymorphism is an important therapeutic and prognostic factor for the use of Pgp-dependent drugs (Kafka et al., 2003). The CT and TT genotypes were equally frequent and exhibited a higher than CC (P=0.02 and 0.07, respectively). When analysing the simultaneous presence of genotypes, the most frequent combination was heterozygous and mutant genotypes (3435CT/1236CT - 21%, 3435TT/1236TT - 27%); in the study by Naumovska et al. (2014), heterozygous (31.78%) and homozygous combinations, but the rate of wild-type allele combination was also high - 21.5% (Naumovska et al., 2014).

In summary, when prescribing drug treatment, it is necessary to pay special attention to the genotype of the patient. For example, non-small-cell lung cancer patients with the T3435T genotype are significantly more likely to develop side effects (Luo et al., 2019). According to Russian authors, the presence of the same genotype increases response to antihypertensive therapy with amlodipine (Sychev et al., 2017). In a study by Tryggvadottir and others, the 3435CC genotype correlates with higher P-gp expression and function compared to the 3435CT or 3435TT genotypes (Tryggvadottir et al., 2018). Thus, patients with the

3435TT genotype can be expected to develop minimal resistance to chemotherapy compared with patients with the 3435CC genotype, so less drug is required to eliminate cancer cells (Tryggvadottir et al., 2018). Studies with tacrolimus and sirolimus showed that, compared with the 3435 CC genotype, patients with the 3435 TT genotype had higher immunosuppression, as evidenced by decreased circulating levels of the inflammatory cytokine, interleukin-2 (IL-2) (Wang et al., 2005).

Pharmacogenetic analysis of ABCB1 gene polymorphisms in addition to other xenobiotic-metabolizing enzymes can help personalize and optimize drug therapy, as this transporter plays a key role in determining the bioavailability of a drug.

Conclusion

We observed a high frequency of altered alleles for the polymorphisms rs1128503 (C1236TT) and rs1045642 (C3435T) of the ABCB1 gene among healthy volunteers of the population of the Tashkent region of Uzbekistan, taking into account their potential effects on expression and activity of P-gp. Thus, it is necessary to expand such studies to select the optimal individualized therapy for many diseases, especially cancer.

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