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Genotype and allele frequencies of *SLCO1B1 g.89595 T>C* polymorphism in a healthy Turkish population

Zuhal UÇKUN ŞAHİNOĞULLARI [1]*, Necmiye CANACANKATAN [2], Mehmet CANACANKATAN [3]

1 Department of Pharmaceutical Toxicology, Faculty of Pharmacy, Mersin University, Mersin, Turkey.
2 Department of Biochemistry, Faculty of Pharmacy, Mersin University, Mersin, Turkey.
3 Mersin City Training and Research Hospital, Emergency Service, Mersin, Turkey.
* Corresponding Author. E-mail: uckunzuhal@gmail.com (Z.U.S.); Tel. +90-324-341 25 18.

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ABSTRACT: Many xenobiotic and endogenous compounds are transported from blood into hepatocytes mediated by organic anion transporter protein (OATP1B1), which is encoded by solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene. Genetic polymorphisms in *SLCO1B1* gene can affect in pharmacokinetics of most compounds and may cause changes in drug efficacy and advers reactions. Thus, genetic polymorphism analysis of genes that may affect the pharmacokinetics of compounds is extremely important. The goal of this study was to determine the genotype and allele frequencies of *SLCO1B1 g.89595* T>C polymorphism in a healthy Turkish population and also to compare our results with the findings of other previously reported populations. Genotyping analyses of *SLCO1B1 g.89595* T>C polymorphism was carried out in 68 healthy Turkish volunteers by a polymerase chain reaction-restriction fragment length polymorphism method. The frequencies of the *TT*, *TC*, and *CC* genotypes were 77.9, 19.1 and 3.0, respectively. Also, the frequencies of *T* and *C* alleles were 87.5 and 12.5, respectively. The genotype frequencies were consistent with Hardy–Weinberg equilibrium. The results of the study are compared with those of other ethnic groups, and they displayed pronounced ethnic group differences, especially East Asian and Southeast ancestry. The detection of *SLCO1B1* polymorphisms may ensure benefits for adjustment of dosage regimens of some drugs and protecting from and/or decreasing adverse events, and also for future studies concerning *SLCO1B1* transporter and its polymorphisms.

KEYWORDS: *SLCO1B1*; drug transporter; genetic polymorphism; Turkish population.

1. INTRODUCTION

There are several factors that can affect the response to drugs, including intrinsic (non-genetic and genetic) and extrinsic factors (diet, smoking, etc.) [1]. It is estimated that genetics variation is responsible for 20 to 95% of variability in drug disposition and effects [2,3]. Drug transporters regulate the absorption, distribution, elimination of drugs by controlling the efflux and influx of drugs in cells, and also accumulating proofs demonstrate that genetic polymorphisms of transporters may have important effects on drug safety, drug efficacy, drug disposition [1].

Solute carrier organic anion transporter family member 1B1 (*SLCO1B1*) gene which has alternative names SLC21A6, LST1, OATPC, OATP2 encodes organic anion transporter protein (OATP1B1) which is a membrane-bound sodium-independent protein [4]. OATP1B1 is particularly expressed in the human basolateral hepatocyte membrane [5], where it mediates active intracellular hepatic transport of diverse anionic substrates [4,6]. OATP1B1 is responsible for the hepatocellular uptake of not only xenobiotics like HIV protease inhibitors, HMG-CoA reductase inhibitors (statins) but also endogenous substrates like thyroid hormones, bile acids [6,7]. Some of these substrates are listed in Table 1.

SLCO1B1 gene is located on chromosome 12 and encodes a 691 amino acid protein with 12 transmembrane helices, and also the gene has 15 exons and 190 common variants with minor allele frequency greater than 5% [4,6]. Many polymorphisms are identified for the human *SLCO1B1* gene. One of these variant is *SLCO1B1 g.89595 T>C* polymorphism (rs4363657, intron 11). This polymorphism is reported to have almost complete linkage disequilibrium with *SLCO1B1* c.521T>C (rs4149056) which is one of the most common variants of *SLCO1B1* gene, but the linkage disequilibrium between these polymorphisms may differ between ethnicities [5].

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OATP1B1 protein has been declared to play a part in general drug disposition [8] and statin pharmacokinetics [9]**.** *SLCO1B1* that is a significant pharmacogene is an important pharmacokinetic gene because OATP1B1 plays a significant part in transporting drugs from blood into hepatocytes [6]. Polymorphisms in the *SLCO1B1* gene have been shown to effect *in vitro* transport function and the pharmacokinetic profile of compounds [10]. Polymorphisms in the gene that encode this protein may be related with disrupted transporter function. This can cause important inter- and intra-population variations in drug efficacy and adverse reactions.

It is known that the genotypic and allelic frequencies of *SLCO1B1* polymorphisms change importantly between dissimilar populations worldwide [11]. However, to the best of our knowledge, there are no studies on this polymorphism in the Turkish population. Hence, the purpose of this study was to detect the genotypic and allelic frequencies of the *SLCO1B1 g.89595 T>C* polymorphism in a healthy Turkish population and also compare our findings with the findings of other previously reported population's studies.

Table 1. Some endogenous or xenobiotics substrates transported by OATP1B1[a].

Endogenous or xenobiotic substrates	Categorize	Substrates
Endogenous	Bile acid	Taurocholic acid
Endogenous	Bile acid	Cholic acid
Endogenous	Eicosanoid	Prostaglandin E2
Endogenous	Eicosanoid	Thromboxane B2
Endogenous	Conjugated steroid	Estradiol-17beta-glucuronide
Endogenous	Thyroid hormones	Thyroxine (T4)
Endogenous	Thyroid hormones	Triiodothyronine (T3)
Xenobiotic	HMG CoA reductase inhibitor	Pravastatin
Xenobiotic	HMG CoA reductase inhibitor	Cerivastatin
Xenobiotic	HMG CoA reductase inhibitor	Pitavastatin
Xenobiotic	HMG CoA reductase inhibitor	Rosuvastatin
Xenobiotic	HIV protease inhibitor	Darunavir
Xenobiotic	HIV protease inhibitor	Saquinavir
Xenobiotic	Antibiotic	Benzylpenicillin
Xenobiotic	ACE inhibitor	Enalaprilat
Xenobiotic	Antidiabetic agent	Repaglinide
Xenobiotic	Thiazolidinediones	Troglitazone sulfate
Xenobiotic	Chemotherapeutic agent	Methotrexate
Xenobiotic	Exogenous toxin	Arsenic

[a]Adapted from Oshiro et al. [6] and Niemi et al. [7].

2. RESULTS

Analysis of the frequencies of the *SLCO1B1 g.89595 T>C* alleles and genotypes was carried out with 68 healthy unrelated individuals. As illustrated in Table 2**,** of the sixty-eight subjects, 45 (66 % of them) were female, while 23 (34 % of them) were male. The body weight of the subjects participating in the study ranged 50 - 107 kg and their mean body weights with standard deviation was 69.00 ± 13.01 kg. The body mass index (BMI) of the subjects varied from 17.51 to 33.69 kg/m^2 and their mean BMI with standard deviation was 24.10 ± 3.63 kg/m^2. In addition, 52 subjects (76%) were <40 years of age, while 15 subjects (24%) were ≥40 years of age.

As demonstrated in Table 3, the frequencies of the *TT*, *TC*, and *CC* genotypes in *SLCO1B1 g.89595* polymorphism were 77.9, 19.1 and 3.0, respectively. Based on these results, the frequencies of *T* and *C* alleles were 87.5 and 12.5, respectively. These results were consistent with the expected genotype distributions, calculated using the Hardy–Weinberg equilibrium (p>0.05).

Table 2. Basic characteristic of the subjects participating in the study.

Demographic	n	%
Gender		
Female	45	66
Male	23	34
Age range		
<40	52	76
≥40	16	24
	Mean±SD	**Range (mix-max)**
Body Weight (kg)	69.00 ± 13.01	50 - 107
BMI (kg/m²)	24.10 ± 3.63	17.51 – 33.69

BMI: Body mass index

Table 3. Distribution of genotypic and allelic frequencies of *SLCO1B1 g.89595 T>C* polymorphism in Turkish population.

Genotype	n (Observed)	Genotype frequencies, %	n (Expected)	Allele frequencies, %
TT	53	77.9	52	T: 87.5
TC	12	19.1	14.9	C: 12.5
CC	3	3.0	1.1	X^2: 1.08 df = 1; p>0.05
Total	68	100	68	

3. DISCUSSION

Allele and genotype frequencies of *SLCO1B1 g.89595 T>C* polymorphism were determined in a healthy Turkish population and the results were compared with other population frequencies in this study. To our knowledge, this is the first investigation to detect this polymorphism in Turkish population. The genotype frequencies of *SLCO1B1* polymorphism were 77.9% for *TT*, 19.1% for *TC*, 3.0% for *CC* genotypes, while the frequencies of *T* and *C* alleles were 87.5% and 12.5, respectively.

The comparison of our results with those of Hapmap Project [12] and other studies [4,5,11,13] is illustrated in Table 4. The genotype and allele frequencies of Turkish population demonstrated prominent dissimilars when compared to East Asian and Southeast ancestry. The allele frequencies of *C* variant were found to be significantly more common in Thai (p<0.001), Southern Han Chinese (CHS) (p<0.001), Kinh in Ho Chi Minh City in Vietnam (KHV) (p<0.001), Chinese Dai in Xishuangbanna (CDX) (p<0.001) and also Amerindian (p<0.05) compared to Turkish population. The *C* variant allele frequencies in these populations vary between 37.2% and 53.8% and thus are predominantly higher compared to other populations. On the other hand, no significant distinctions were noted between Turkish population and South Asian, including Bengali in Bangladesh (BEB), Punjabi in Lahore, Pakistan (PJL) and Indian Telugu in the UK (ITU) (p>0.05). The *C* allele frequencies ranged 7.8 - 14.5 % in these populations.

Interestingly, among European ancestry, it was observed that there were statistically significant differences between Toscani in Italy (TSI) (p<0.05), Finnish in Finland (FIN) (p<0.001) and Turkish population in terms of *C* variant allele frequency. On the other hand, the *C* allele frequencies in Turkish population were similar to those reported for White ancestry including Caucasian descent, Hungarian, Roma, Czech, British in England and Scotland (GBR), Iberian populations in Spain (IBS), Colombian in Medellin in Colombia (CLM), Mexican Ancestry in Los Angeles in California (MXL), Peruvian in Lima in Peru (PEL), Puerto Rican in Puerto Rico (PUR). The *C* allele frequencies in these populations ranged 10.2 - 19.8 %. Furthermore, there were similarities between Turkish population and Black ancestry including African descent, Yoruba in Ibadan in Nigeria (YRI), African Ancestry in Southwest US (ASW), Esan in Nigeria (ESN), Luhya in Webuye, Kenya (LWK) (p>0.05) in terms of *C* allele frequencies (Table 4). The *C* allele frequencies in these populations vary between 10.8% and 18.0%.

Table 4. Genotype and allele frequencies of *SLCO1B1 g.89595 T>C* in different ethnic populations.

Ethnicity	Population	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		References
			TT	*TC*	*CC*	*T*	*C*	
White								
	Caucasian descent	603	433 (71.8)	154 (25.5)	16 (2.7)	1020 (84.6)	186 (15.4)	Santos et al. [11]
European	Turkish	68	53 (77.9)	13 (19.1)	2 (3.0)	119 (87.5)	17 (12.5)	The present study
	Hungarian	442	285 (64.5)	141 (31.9)	16 (3.60)	711 (80.4)	173 (19.6)	Nagy et al. [4]
	British in England and Scotland (GBR)	91	65 (71.4)	25 (27.5)	1 (1.1)	155 (85.2)	27 (14.8)	Hapmap Project [12]
	Iberian populations in Spain (IBS)	107	81 (75.7)	25 (23.4)	1 (0.9)	187 (87.4)	27 (12.6)	Hapmap Project [12]
	Roma	470	308 (65.5)	150 (31.9)	12 (2.60)	766 (81.5)	174 (18.5)	Nagy et al. [4]
	Czech	2267	1449 (63.9)	736 (32.5)	82 (3.6)	3634 (80.2)	900 (19.8)	Hubáček et al. [13]
	Toscani in Italy (TSI)*	107	63 (58.9)	40 (37.4)	4 (3.7)	166 (77.6)	48 (22.4)	Hapmap Project [12]
	Finnish in Finland (FIN)**	99	48 (48.5)	43 (43.4)	8 (8.1)	139 (70.2)	59 (29.8)	Hapmap Project [12]
American	Colombian in Medellin, Colombia (CLM)	94	61 (64.9)	29 (30.9)	4 (4.3)	151 (80.3)	37 (19.7)	Hapmap Project [12]
	Mexican Ancestry in Los Angeles, California (MXL)	64	52 (81.2)	11 (17.2)	1 (1.6)	115 (89.8)	13 (10.2)	Hapmap Project [12]
	Peruvian in Lima, Peru (PEL)	85	57 (67.1)	25 (29.4)	3 (3.5)	139 (81.8)	31 (18.2)	Hapmap Project [12]
	Puerto Rican in Puerto Rico (PUR)	104	68 (65.4)	35 (33.7)	1 (1.0)	171 (82.2)	37 (17.8)	Hapmap Project [12]

Table 4. Genotype and allele frequencies of *SLCO1B1 g.89595 T>C* in different ethnic populations (continues).

Ethnicity	Population	Sample size	Genotype frequencies n (%)			Allele frequencies n (%)		References
			TT	*TC*	*CC*	*T*	*C*	
Asians								
	Amerindian *	182	99 (54.4)	71 (39.0)	12 (6.6)	269 (73.9)	95 (26.1)	Santos et al. [11]
Southeast Asian	Thai **	391	161 (41.2)	169 (43.2)	61 (15.6)	491 (62.8)	291 (37.2)	Kaewboonlert et al. [5]
East Asian	Southern Han Chinese, China (CHS)**	105	31 (29.5)	53 (50.5)	21 (20.0)	115 (54.8)	95 (45.2)	Hapmap Project [12]
	Kinh in Ho Chi Minh City, Vietnam (KHV)**	99	31 (31.3)	48 (48.5)	20 (20.2)	110 (55.6)	88 (44.4)	Hapmap Project [12]
	Chinese Dai in Xishuangbanna, China (CDX)**	93	17 (18.3)	52 (55.9)	24 (25.8)	86 (46.2)	100 (53.8)	Hapmap Project [12]
South Asian	Bengali in Bangladesh (BEB)	86	64 (74.4)	19 (22.1)	3 (3.5)	147 (85.5)	25 (14.5)	Hapmap Project [12]
	Punjabi in Lahore, Pakistan (PJL)	96	82 (85.4)	13 (13.5)	1 (1.0)	177 (92.2)	15 (7.8)	Hapmap Project [12]
	Indian Telugu in the UK (ITU)	102	85 (83.3)	16 (15.7)	1 (1.0)	186 (91.2)	18 (8.8)	Hapmap Project [12]
Black								
	African descent	97	76 (78.4)	21 (21.6)	0	173 (89.2)	21 (10.8)	Santos et al. [11]
African	Yoruba in Ibadan, Nigeria (YRI)	108	81 (75.0)	25 (23.1)	2 (1.9)	187 (86.6)	29 (13.4)	Hapmap Project [12]
	African Ancestry in Southwest US (ASW)	61	42 (68.9)	16 (26.2)	3 (4.9)	100 (82.0)	22 (18.0)	Hapmap Project [12]
	Esan in Nigeria (ESN)	99	76 (76.8)	21 (21.2)	2 (2.0)	173 (87.4)	25 (12.6)	Hapmap Project [12]
	Luhya in Webuye, Kenya (LWK)	99	68 (68.7)	29 (29.3)	2 (2.0)	165 (83.3)	33 (16.7)	Hapmap Project [12]

Differences in genotype and allele frequencies were examined by X^2 test. n total number of subjects.
Significant at *p< 0.05 and **p < 0.001 when compared the present study.

As agreed from the above results, the frequencies of *SLCO1B1* polymorphism can change importantly from population to population worldwide. Thus, this can cause important inter- and intra-population variations in drug response, drug efficacy and adverse reactions. It is known that many clinically used drugs can be transported from blood into liver mediated by OATP1B1 that is encoded by the *SLCO1B1* gene polymorphism, and OATP1B1-dependent transport is a significant step in mediating drug hepatic clearance [4,6]. Most of the studies on the association of the *SLCO1B1* gene polymorphisms with drugs are related to statins, which are among the best-selling drugs worldwide [14]. Generally, statins are well tolerated [15]. However, these drugs can give rise to myopathy with signs that range from slight myalgia to rhabdomyolysis [14]. In a clinical study of 12000 patients taking simvastatin at a dose of 80 mg/day that has assessed relationship between gene polymorphisms and myopathy during statin treatment, it was reported that for *SLCO1B1 g. 89595 T>C* polymorphism, the odds ratio for myopathy was 4.5 (95% confidence interval 2.6-7.7) per copy of the C allele, and also this ratio was 16.9 (95% confidence interval 4.7-61.1) in subjects with CC genotypes in comparison with subjects with TT genotypes [16]. In a case report declared by Notarangelo et al. [14], there were two cases, both of which were male. Patient 1 was 48 years old, patient 2 was 65 years old and also patient 2 was patient 1's father. Patient 1, history of coronary artery disease, suffered from quickly developing muscle pain and weakness of the extremities during therapy with 40 mg atorvastatin. In addition, patient 2 had similar symptoms as his son. It was observed that in both cases, symptoms disappeared after discontinuation of atorvastatin. These two patients were determined to be the carriers of the *SLCO1B1* rs4363657 polymorphism.

Contrary to the above results, there are also studies in which polymorphism has no effect on statin side effects. In the study conducted by Hubacek et al. [13], *SLCO1B1* rs4363657 polymorphism was determined in two groups of dyslipidemia patients cured with atorvastatin or simvastatin at 10 or 20 mg/day, including subgroup who had myalgia induced by statin (n=286), and subgroup who had not myalgia/myopathy (n=707), and in control population who had not lipid-lowering therapy (n=2301). They observed that no significant was distinction among three groups for genotype frequencies of *SLCO1B1*, and also there was no relationship between rs4363657 polymorphism in *SLCO1B1* and risk of myalgia/myopathy in low doses of statin-treated Czech patients. In addition, Kaewboonlert et al. [5] reported that there was no relationship between *SLCO1B1 g.89595 T>C* polymorphism and lipid-lowering response to 3 and 12 months of 20 or 40 mg/day simvastatin treatment in Thai patients with hypercholesterolaemia (n=391). It has been concluded that in lipid-lowering response to simvastatin treatment in Thai patients with hypercholesterolaemia, *SLCO1B1 g.89595 T>C* polymorphism should not be employed as the genetic markers.

Differences between ethnic groups may affect in individual variability, and individual variability in drug safety and efficacy is a main problem in present clinical practice, drug regulation, drug development [1,2]. Genetic polymorphisms may make significant contributions to individualization of drug dosages, disease management, and improved therapeutics [3].

4. CONCLUSION

We present evidence of the distribution of genotype and allele frequencies of *SLCO1B1* polymorphism in a healthy Turkish population. The detection of polymorphisms in the mentioned gene may have benefits for adjustment of dosage regimens of some drugs and prevention from xenobiotics for precluding and decreasing adverse events, and also for future studies concerning *SLCO1B1* transporter and its polymorphisms.

5. MATERIALS AND METHODS

5.1. Subjects

The current investigation was performed on unrelated sixty-eight Turkish healthy volunteers. The blood samples for the study were collected in Mersin City Training and Research Hospital, Mersin, Turkey. The study was approved by the Ethics Committee of Mersin University (22/10/2015, protocol no: 2015/317) and was executed according to Good Clinical Practices and the Helsinki declaration. The informed consent was taken from all the subjects who participated in the current investigation. Basic characteristics of the subjects are indicated in Table 2.

5.2. Blood sampling and DNA extraction

Blood samples of unrelated, healthy volunteers were collected vacutainer in tubes containing heparin between 08: 00 and 10: 30 a.m. Genomic DNA extraction was performed using the Thermo Scientific Genomic DNA Purification Kit (ThermoFisher) as per the manufacturer's directives. DNA yields were detected through measurement of the absorbance at 260 nm (A260). The samples to be studied were kept at -80°C up to analysis.

5.3. Genotyping

SLCO1B1 g.89595 T>C polymorphism was performed with the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method defined by Nagy *et al.* [4] with slight modifications. Briefly, PCR amplification for *SLCO1B1* was done using the forwad and reverse primers: 5'-CAGTTTGCTAGTGTTTTGTTGAG-3' and R:5'-ACCATCCAAGACGAACAAAGAG-3', respectively. PCR was performed in a 50-µl reaction mixture which contained 400 to 600 ng of genomic DNA, 10 x PCR buffer, 1.25 mM each deoxynucleotide triphosphate, 20 ng of each primer, 1.00 unit of Taq polymerase, and 1.25 mM $MgCl_2$ (Fermentase) on the Thermal Cycler (Thermo, UK). The PCR process was as follows: 96 ˚C for 2 min for initial denaturation, and then 35 cycles of 95°C for 30 sec, 53 °C for 30 sec, 72 ˚C for 30 sec, followed by a final elongation at 72°C for 5 min. In order to ensure the use of contaminant DNA-free reagents, each PCR analysis included negative control reactions. PCR products (369 bp) were electrophoresed on a 2 % agarose gel including ethidium bromide (500 ng/ml) which made the products visible, and then the 10 µl PCR product was cut in 15 minutes at 37°C using 10 U of Fast Digest Kpn I restriction enzyme with the proper buffer in total volume of 20 µl. The T allele was digested to 236 and 133 bp fragments while the C allele was digested to 152, 133 and 84 bp on 3 % agarose gel with ethidium bromide was used to evaluate the digested fragments. For a quality assurance, 10% of the samples at random was reanalyzed, which provide 100% concordance.

5.4. Statistical analysis

Allelic and genotypic frequencies were calculated using genotype counting method. The expected and observed frequencies of *SLCO1B1* gene were compared using the chi-square (X^2) test based on Hardy–Weinberg equilibrium. X^2 test was employed to compare the genotype and allele frequencies determined from the current investigation with those in other populations. Statistical analysis were performed using IBM SPSS computer software for Windows 25.0. $p<0.05$ and <0.001 were accepted statistically significant.

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