ABSTRACT

As a membrane influx transporter, organic anion-transporting polypeptide 1B1 (OATP1B1) regulates the cellular uptake of a number of endogenous compounds and drugs. The aim of this study was to characterize the diversity of the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene encoding this transporter in two ethnic groups populating the Western Balkans. The distribution of SCLO1B1 alleles was determined at seven variant sites (c.388A>G, c.521T>C, c.571T>C, c.597C>T, c.1086C>T, c.1463G>C and c.*439T>G) in 266 Macedonians and 94 Albanians using the TaqMan allelic discrimination assay. No significant difference in the frequencies of the single nucleotide polymorphisms (SNPs) was observed between these populations. The frequency of the c.521T>C SNP was the lowest (<13.7 and 12.2%, respectively), while the frequencies of all other SNP alleles were above 40.0%. Variant alleles of c.1463G>C and c.1086C>T SNPs were not identified in either ethnic group. The haplotype analysis revealed 20 and 21 different haplotypes in the Macedonian and Albanian population, respectively. The most common haplotype in both ethnic groups, *1J/*1K/*1L, had a frequency of 39.0% and 26.6%, respectively. In both populations, the variant alleles of the functionally significant c.521T>C and c.388A>G SNPs existed in one major haplotype (*15/*16/*17), with a frequency of 8.6 and 2.4% in the Macedonian and Albanian subjects, respectively. In conclusion, sequence variations of the SLCO1B1 gene in the studied populations occur at high frequencies, which are similar to that of the Caucasian population. Further studies are needed to evaluate the clinical significance of these SNPs and/or the major SLCO1B1 haplotypes they form for a large number of substrates and for susceptibility to certain diseases.

Keywords: Haplotypes; organic anion-transporting polypeptide 1B1 (OATP1B1); solute carrier organic anion-transporter family member 1B1 (SLCO1B1) gene; single nucleotide polymorphisms (SNPs); Western Balkan populations.

INTRODUCTION

Membrane influx and efflux transporters have a significant role in facilitating or preventing drug movement through biological membranes. Drug responses are largely dependent on their interplay with...
SNPs OF THE SLCO1B1 GENE

phases I and II metabolism and the physicochemical properties of a drug. They function in the selective absorption and elimination of drugs, mediate tissue-specific drug distribution and are also targets of many clinically used drugs. In addition, they play a critical role in the development of resistance to anticancer drugs, anticonvulsants and antiviral agents. When considering drug transport, two major super-families, ABC (ATP binding cassette) and SLC (solute carrier) transporters attract the highest scientific attention.

The SLC super family includes genes that encode facilitating transporters and ion-coupled secondary active transporters that reside in various cell membranes. Genes of the solute carrier organic anion transporter (SLCO) family encode organic anion-transporting polypeptides (OATPs), membrane influx transporters identified mostly in the intestine, liver, kidney, lung, testes, placenta and blood-brain barrier among other organs. The OATP1B1 [previously OATP2, OATP-C and liver specific transporter 1 (LST-1)], expressed in the sinusoidal membrane of the hepatocytes, is known to be involved in the hepatic uptake of a broad array of endogenous compounds (e.g., steroid conjugates, bile acids, eicosanoids and thyroid hormones) and drugs such as methotrexate, fexofenadine, repaglinide and statins [1-6]. Examples of in vitro OATP1B1 drug substrates include several HMG-CoA reductase inhibitors, angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists [6-8]. Many drugs have also been identified in vitro as OATP1B1 inhibitors and there are some in vivo interactions where OATP1B1 inhibition can be regarded as an important mechanism. Examples include cyclosporine, atorvastatin, gemfibrozil and rifampicin [9,10].

The OATP1B1 protein is a 691-amino acid glycoprotein with 12 putative membrane-spanning domains and a large fifth extracellular loop. Its encoding gene, solute carrier organic anion transporter family member 1B1 (SLCO1B1), is located on chromosome 12 (gene locus 12p12) [11]. A large number of single nucleotide polymorphisms (SNPs), both non synonymous and synonymous, have been discovered in the SLCO1B1 gene, and several of these have been proven to affect a substrate-dependent transport function in vitro and in vivo [12,13]. While no firm evidence for association between these SNPs and development of certain diseases (e.g., gallstone development, essential hypertension) due to dysregulation of endogenous compounds transport exists, there are numerous research data pointing to their effects on drugs responses.

The SNPs 388 (A>G) (*1b, rs2306283) and 521 (C>T) (*5, rs4149056) are considered to be the most prevalent and most relevant variants, encoding a substitution of alanine for valine at amino acid 174 (p.Val174Ala), and amino acid change at position 130 (p.Asn130Asp), respectively. Increased transport activity of pravastatin as well as decreased plasma concentration of ezetimibe in carriers of the SLCO1B1*1b allele was observed [14,15], unlike reduced uptake of all statins except fluvastatin in hepatocytes and increased area under curve (AUC) of fexofenadine, repaglinide and irinotecan in carriers of SLCO1B1*5 [3,4,16,17]. The carriers of the c.521T>C variant were also highlighted by a genome-wide association study as a population with an increased risk for simvastatin-induced myopathy because of the increased plasma and muscle exposure to statins [18]. These findings were further confirmed by Santos et al. [19], who suggested that the SLCO1B1 genetic risk depends on the specific drug that was used. It was also shown that subjects carrying the SLCO1B1 c.388GG genotype exhibit significantly higher low-density-lipoprotein cholesterol reduction relative to c.388AA+ c.388AG carriers, pointing out that the SLCO1B1 c.388A>G polymorphism may be used as an important marker for predicting the efficacy of a lipid-lowering therapy [20].

Recent data point out that these two variants are in linkage disequilibrium (LD) and exist in variable SLCO1B1 haplotypes; AT, a haplotype known as *1A (reference haplotype), GT as *1B, AC as *5 and GC as *15, for c.388A>G and c.521T>C, respectively [13]. The *15 haplotype has been consistently associated with a decreased transport activity, while controversial results have been reported for the *1B haplotype [21]. It was also demonstrated that the SLCO1B1*17 haplotype (g.-11187G>A, c.388G>A and c.521T>C) was associated with increased plasma concentrations of pravastatin in humans [22], while the *14 haplotype (c.388G>c.463A-c.521T) was characterized with enhanced response to fluvastatin [23].

It is becoming evident that the incidence of sequence variations in the SLCO1B1 gene is largely dependent on the ethnic background. The c.521T>C variant showed an allele frequency of approximately 10.0-15.0% in Asian populations, 10.0-20.0%
in Caucasians and 1.0-2.0% in African-American populations. The c.388A>G SNP showed an allele frequency of approximately 30.0-45.0% in Caucasians, 70.0-80.0% in African-American/Sub-Saharan African populations and 60.0-90.0% in Asian populations [12,22,24-26]. Therefore, characterization of the genetic variation in this transporting gene is an important step towards understanding the individual variation in drugs-substrates responses and developing a personalized and safer drug therapy.

To the best of our knowledge, there is no evidence about genotyping of OATP1B1 in the populations living in Western Balkans. Also, there is no evidence when considering the populations living in the whole Balkan Peninsula, with exception of one report evaluating association between three SLCO1B1 SNPs and statin response in the Greek population [27]. In this respect, there has not been any report on the genotype of SLCO1B1 allelic variants in Macedonian and Albanian populations who are considered Caucasians. The origin of the Macedonians and Albanians is a continuing matter of discussion among historians; they also showed unequivocal signs of a common genetic history. In addition, Western Balkan countries have always been a historical crossroads between Asia, Africa and Europe. Considering all the above, the overall aim was to analyze the diversity of the SLCO1B1 gene in selected ethnically diverse populations living in the Western Balkans [Republic of Macedonia (RoM) and Republic of Kosovo (RoK)]. In this article, the results from the allele and genotypic frequencies of the several known SNPs in the SLCO1B1 gene and the haplotypes they form are presented. The results from this study could serve as a baseline clinical data for dosing of all drugs substrates of OATP1B1 and avoiding the adverse drug reactions.

**MATERIALS AND METHODS**

**Subjects and Study Protocol.** For the aim of this study, a total of 233 Caucasian patients (age 18-72 years, average body mass index (BMI) 26.20 kg/m², 109 women and 124 men) with hypercholesterolemia type IIa or IIb, were selected randomly from the outpatients evaluated for coronary heart disease at the University Clinic of Cardiology in Skopje (RoM) and the University Clinical Center in Pristina, Clinic for Internal Diseases (RoK). Of these, 156 (66.95%) were Macedonians, 64 (27.47%) Albanians, four (1.72%) Turks and nine (3.86%) Gypsies. Due to the low number of patients, the data for the groups of Turks and Gypsies are not presented in this paper. Therefore, the evaluated group of patients (220 individuals, 105 female and 115 male patients) consisted of 70.91% Macedonians (n = 156, 73 women and 83 men) and 29.09% Albanians (n = 64, 32 women and 32 men).

Initially, the study protocol was approved by the Ethics Committee of the Faculty of Pharmacy and Committee for Clinical Studies of the Faculty of Medicine, University “Ss. Cyril and Methodius” (UKIM), Skopje, RoM, and the Ethics Committee and Committee for Clinical Studies of the Faculty of Medicine, University in Pristina, RoK. All participants received oral and written information and gave a written informed consent before entering the study. Exclusion criteria (note: not relevant for the results present in this study, but important for the overall aim of the research) included cancer in remission for period shorter than 5 years, Cushing syndrome, hyperthyroidism, positive hepatitis B surface antigen, hepatitis C virus antibody, fibromyalgia, myopathy, rhabdomyolysis, malabsorption syndrome, renal failure, liver disease, McArdle disease, women who are pregnant, nursing or have planned a pregnancy, drugs interacting at the level of SLCO1B1. Data for BMI, cigarette smoking, blood pressure, alcohol consumption, physical activity and pharmacotherapy were also collected and recorded. To evaluate the frequency of genetic variations in genes encoding SLCO1B1, one blood sample was obtained from each participant for DNA extraction on the first day of the hospital visit.

In this study, 140 DNA samples obtained from the DNA bank of the Center for Biomolecular Analysis at the UKIM-Faculty of Pharmacy, Skopje, RoM, were also analyzed for the diversity of the SLCO1B1 gene. These samples were obtained from healthy individuals (of Caucasian ethnicity, 78.57% Macedonians, 21.43% Albanians, 79 males, average age 48.0 ± 12.9, BMI 26.16 kg/m²) selected by medical history, physical examination and routine laboratory tests before entering the study. Considering that there was no significant difference (p>0.05) in the allelic frequencies of SLCO1B1 variants and genotype distributions between healthy subjects and patient groups, statistical analysis was also performed on the total population consisted of 360 subjects, of which 73.89% were Macedonians (n = 266, 129
women and 137 men) and 26.11% Albanians (n = 94, 42 women and 52 men).

Genomic DNA Extraction and Genotyping Procedures. Three mL venous blood samples drawn with EDTA as anticoagulant were collected and stored at 4 °C prior to DNA isolation. DNA isolation was performed at the Center for Biomolecular Pharmaceutical Analyses, UKIM-Faculty of Pharmacy, Skopje, RoM, using the Qiamp DNA Blood kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer’s protocol. The samples were kept at –20 °C until further analysis. The SLCO1B1 SNPs to be genotyped were selected on the basis of literature data [6,13,20,28,29] and a previous study in which 151 subjects were included [30]. The following variants in the SLCO1B1 gene were analyzed: c.388A>G (Asn130Asp, rs2306283), c.521T>C (Val174Ala, rs4149056), c.571T>C (Leu191Leu, rs414 9057), c.597C>T (Phe199Phe, rs2291075), c.1086C>T (Tyr362Tyr, rs57040246), c.1463G>C (Gly488Ala, rs3950 2379), c.*439T>G (rs419087), the position is given with the first nucleotide 3’ of the stop codon (TAA) set to *.1 using TaqMan allelic discrimination assay (Applied Bio-systems, Foster City, CA, USA).

Polymerase chain reaction was performed on the quantitative real-time PCR (q-PCR) system Mx3005P (Strata gene, La Jolla, CA, USA) using TaqMan genotyping protocols (TaqMan®Drug Metabolizing assay; Applied Bio-systems) in total volume of 12.5 µL under following conditions: one cycle of 2 min. at 50 °C, one cycle of 10 min. at 95 °C, and 50 cycles of 15 seconds at 92 °C and 1 min. at 60 °C.

Population Genetics and Statistical Analysis. The study sample alleles and genotype frequencies were estimated with a gene counting method. The agreement with Hardy-Weinberg equilibrium (HWE) of the observed genotypic distribution for the SLCO1B1 gene was tested with the χ² test. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) software (v. 19.0).

Genetic diversity was quantified by the members of the same ethnic population, between the ethnic populations, and between different ethnic populations and the global population. Population comparisons were also performed with the χ² test of population differentiation. Odds ratios (ORs) were calculated with 95% confidence interval (95% CI). For multiple comparisons, Bonferroni’s post hoc test was used. Statistically significant differences were those where the p value was less 0.05. Linkage disequilibrium for each pair of SNPs within each population was quantified (correlation r² and coefficient of linkage disequilibrium D’ values) to find the haplotypes in the study groups. The statistical analyses were carried out using the SHEsis software platform for the analysis of LD, haplotype construction and genetic association at polymorphism loci (http://analysis2.bio-x.cn/myAnalysis.php) [31]. The haplotypes were presented with their previous assigned names, as cited in the study of Pasanen et al. [13] in which allelic frequencies at 11 variant sites were determined (g.11187G>A, g.11110T>G, g.10499A>C, c.388A>G, c.411G>A, c.463C>A, c.521T>C, c.571T>C, c.597C>T, c.1929A>C and c.*439T>G). Considering that five of these SNPs and two other SNPs have been analyzed in the present investigation, one haplotype has several names and there are haplotypes that we designated as new.

RESULTS

Genotypes and Allele Frequencies. Genetic variation of SLCO1B1 was studied in 360 subjects in total, both patients with hyperlipidemia type IIa or IIb and healthy subjects, of which 266 were of Macedonian and 94 of Albanian ethnicity. Observed genotypes and allelic frequencies of SLCO1B1 gene polymorphisms did not differ significantly (p >0.05) when comparing the data obtained from patients and healthy subjects (Table 1). In addition, the observed frequency distributions did not show significant deviations from HWE (p >0.05) in both populations of the two ethnic groups, the population of both patients and healthy subjects, confirming the random selection of the individuals, i.e., representativeness of the population samples being studied. Taking all this into consideration, genotype and allele frequencies for the total population of Macedonians and Albanians were estimated and the data are presented in Table 2.

Data for distribution of genotypes and allele frequencies of SLCO1B1 gene polymorphisms between females and males, including both patients and healthy subjects within each ethnic group, are presented in Table 3. No significant differences for all SLCO1B1 gene polymorphisms were observed between female and male subjects, both within each and between the two ethnic groups.
Table 1. Allelic and genotypic frequencies of *SLCO1B1* in patients with hyperlipidemia type IIa or IIb and healthy subjects.

| Location/Position/dbSNP ID | Ethnic Group | Macedonian* | Albanian* |
|---------------------------|--------------|-------------|-----------|
|                           | Number of Subjects | Patients (n=156) (%) | Healthy Subjects (n=110) (%) | Patients (n=64) (%) | Healthy Subjects (n=30) (%) |
| Exon 4/c.388A>G/rs2306283 | AA           | 54 (34.6)   | 34 (30.9) | 20 (31.2) | 9 (30.0) |
|                           | AG           | 80 (51.3)   | 58 (52.7) | 35 (54.7) | 16 (53.3) |
|                           | GG           | 22 (14.1)   | 18 (16.3) | 9 (14.1)  | 5 (16.7)  |
|                           | *p* Value*   | 0.77369     |           |           | 0.94636   |
|                           | G allele     | 124 (40.0)  | 94 (42.7) | 53 (41.4) | 26 (43.3) |
|                           | A allele     | 188 (60.0)  | 126 (57.3)| 75 (58.6) | 34 (56.7) |
| Exon 5/c.521T>C/rs4149056 | CC           | 4 (2.6)     | 5 (4.5)  |           | 1 (3.0)   |
|                           | CT           | 36 (23.1)   | 19 (17.3) | 14 (21.9) | 7 (23.3)  |
|                           | TT           | 116 (74.3)  | 86 (78.2) | 50 (78.1) | 22 (73.3) |
|                           | *p* Value*   | 0.38218     |           |           | 0.33055   |
|                           | C allele     | 44 (14.1)   | 29 (13.2) | 14 (11.0) | 9 (15.0)  |
|                           | T allele     | 268 (85.9)  | 191 (86.8)| 114 (89.0)| 51 (85.0) |
| Exon 5/c.571T>C/rs4149057 | CC           | 66 (42.3)   | 45 (41.0) | 22 (34.4) | 12 (40.0) |
|                           | CT           | 71 (45.5)   | 53 (48.2) | 22 (33.1) | 15 (50.0) |
|                           | TT           | 19 (12.2)   | 12 (11.0) | 8 (12.5)  | 3 (10.0)  |
|                           | *p* Value*   | 0.89666     |           |           | 0.84958   |
|                           | C allele     | 203 (65.0)  | 143 (65.0)| 78 (61.0) | 39 (65.0) |
|                           | T allele     | 109 (35.0)  | 77 (35.0) | 50 (39.0) | 21 (35.0) |
| Exon 5/c.597C>T/rs229107  | CC           | 60 (38.5)   | 40 (36.4) | 16 (25.0) | 11 (36.7) |
|                           | CT           | 67 (42.9)   | 50 (45.5) | 35 (54.7) | 14 (46.6) |
|                           | TT           | 29 (18.6)   | 20 (18.2) | 13 (20.3) | 5 (16.7)  |
|                           | *p* Value*   | 0.91693     |           |           | 0.50617   |
|                           | T allele     | 125 (40.1)  | 90 (40.9) | 61 (47.6) | 24 (40.0) |
|                           | C allele     | 187 (59.9)  | 130 (59.1)| 67 (52.3) | 36 (40.0) |
| Exon 8/c.1086C>T/rs57040246| CC           | 156 (100.0) | 110 (100.0)| 64 (100.0)| 30 (100.0)|
|                           | CT           | 0 (0.0)     | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   |
|                           | TT           | 0 (0.0)     | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   |
|                           | *p* Value*   | >0.05       |           |           | >0.05     |
|                           | T allele     | 0 (0.0)     | 0 (0.0)   | 0 (0.0)   | 0 (0.0)   |
|                           | *p* Value*   | >0.05       |           |           | >0.05     |

*Note:* *SLCO1B1* = Solute Carrier Organic Anion Transporter 1B1
Table 2. Genetic variation of the SLCO1B1 gene in Macedonian and Albanian subjects.

| Ethnic Group | Observed Frequency | Expected Frequency by HWE (%) | p Value | Observed Frequency | Expected Frequency by HWE (%) | p Value |
|--------------|--------------------|-------------------------------|---------|--------------------|-------------------------------|---------|
| Position/dbSNP ID | n=266 (%) | n=94 (%) | | n=266 (%) | n=94 (%) | |
| c.388A>G/rs2306283 | | | | | | |
| AA | 88 (33.1) | 34.8 | 0.99737 | 29 (30.8) | 33.6 | 0.99358 |
| AG | 138 (51.9) | 48.4 | | 51 (54.2) | 48.7 | 0.99358 |
| GG | 40 (15.0) | 16.8 | | 14 (14.9) | 17.7 | |
| p Value | 0.91299 | | | | | |
| p Value | 0.80266 | | | | | |
| c.521T>C/rs4149087 | | | | | | |
| GG | 32 (20.5) | 28 (25.45) | 15 (23.4) | 9 (30.0) | | |
| GT | 81 (51.9) | 50 (45.45) | 31 (48.4) | 16 (53.3) | | |
| TT | 43 (27.6) | 32 (29.1) | 18 (28.1) | 5 (16.7) | | |
| p Value | 0.48666 | | | | | |
| p Value | 0.46337 | | | | | |
| 3'UTR/c.*439T>G/rs4149087 | | | | | | |
| GG | 145 (46.5) | 106 (48.2) | 61 (47.7) | 34 (56.7) | | |
| GT | 167 (53.5) | 114 (51.8) | 67 (52.3) | 26 (43.3) | | |
| p Value | 0.69853 | | | | | |
| p Value | 0.24882 | | | | | |

DbSNP: database of single nucleotide polymorphism; 3' UTR: 3' untranslated region; NCBI: National Center for Biotechnology Information.

* Macedonians populating the RoM.
* Albanians populating the RoM and RoK.
* The positions of SNPs are given in relation to the NCBI reference sequences NM_006446.2 (cDNA; c) with the first nucleotide of the ATG first codon set to 1 and the nucleotide 5' of ATG set to −1. The position of c.*439 is given with the first nucleotide 3' of the stop codon (TAA) set to *1.
* The p value for the differences of genotype distributions between the patients and healthy subjects within the ethnic group.
* The p value for the differences of allelic frequencies between the patients and healthy subjects within the ethnic group.
| SNP                  | CC        | CT        | TT        | p Value  |
|---------------------|-----------|-----------|-----------|----------|
| c.571T>C/rs4149057  |           |           |           | 0.61507  |
| C allele            | 346 (65.0)| 117 (62.2)|           |          |
| T allele            | 186 (35.0)| 71 (37.8) |           |          |
| p Value             | 0.49039   |           |           |          |
| c.597C>T/rs229107   |           |           |           | 0.27697  |
| T allele            | 215 (40.4)| 85 (45.2) |           |          |
| C allele            | 317 (59.6)| 103 (54.8)|           |          |
| p Value             | 0.25125   |           |           |          |
| c.1086C>T/rs57040246|           |           |           | >0.05    |
| T allele            | 0 (0.0)   | 0 (0.0)   |           |          |
| C allele            | 0 (0.0)   | 0 (0.0)   |           |          |
| p Value             | >0.05     |           |           |          |
| c.1463G>C/rs59502379|           |           |           | >0.05    |
| C allele            | 0 (0.0)   | 0 (0.0)   |           |          |
| p Value             | >0.05     |           |           |          |
| c.*439T>G/rs4149087 |           |           |           | >0.05    |
| G allele            | 251 (47.2)| 95 (50.5) |           |          |
| T allele            | 281 (52.8)| 93 (49.5) |           |          |
| p Value             | 0.42917   |           |           |          |

HWE: Hardy-Weinberg equilibrium; dbSNP: database of single nucleotide polymorphism; 3'UTR: 3' untranslated region; NCBI: National Center for Biotechnology Information.

* Macedonians populating the RoM.
* Albanians populating the RoM and RoK.
* The p value for the differences between observed and expected frequencies of genotype distributions within the ethnic group.
* The positions of SNPs are given in relation to the NCBI reference sequences NM_006446.2 (cDNA; c.) with the first nucleotide of the ATG first codon set to 1 and the nucleotide 5' of ATG set to –1. The position of c.*439 is given with the first nucleotide 3' of the stop codon (TAA) set to *1.
* The p value of differences in genotype distributions between the ethnic groups.

The p value of allele frequencies between the ethnic groups.
Table 3. Distribution of genotype and allele frequencies of the *SLCO1B1* gene polymorphisms in female and male groups separately, within each ethnic group.

| Ethnic Group | **Macedonian** | **Albanian** |
|--------------|----------------|-------------|
| Number of Subjects | Females (n=129) (%) | Males (n=137) (%) | Females (n=42) (%) | Males (n=52) (%) |
| Position/dbSNP ID | | | | |
| c.388A>G/rs2306283 | | | | |
| AA | 42 (32.6) | 46 (33.6) | 14 (33.3) | 15 (28.8) |
| AG | 65 (50.4) | 73 (53.3) | 24 (57.1) | 27 (51.9) |
| GG | 22 (17.0) | 18 (13.1) | 4 (9.5) | 10 (19.2) |
| p Value<sup>a</sup> | 0.66841 | | 0.41932 | |
| G allele | 109 (42.2) | 109 (39.8) | 32 (38.1) | 47 (45.2) |
| A allele | 149 (57.8) | 165 (60.2) | 92 (61.9) | 57 (54.8) |
| p Value<sup>b</sup> | 0.56309 | | 0.32702 | |
| c.521T>C/rs4149056 | | | | |
| CC | 6 (4.6) | 3 (2.2) | – | 1 (2.0) |
| CT | 25 (19.4) | 30 (21.9) | 9 (21.4) | 12 (23.1) |
| TT | 98 (76.0) | 104 (75.9) | 33 (78.6) | 39 (75.0) |
| p Value<sup>a</sup> | 0.49822 | | 0.64576 | |
| C allele | 37 (14.3) | 36 (13.1) | 9 (10.7) | 14 (13.5) |
| T allele | 221 (85.7) | 238 (86.9) | 75 (89.3) | 90 (86.5) |
| p Value<sup>b</sup> | 0.68707 | | 0.56765 | |
| c.571T>C/rs4149057 | | | | |
| CC | 53 (41.2) | 58 (42.3) | 14 (33.3) | 20 (38.5) |
| CT | 61 (47.3) | 63 (46.0) | 23 (54.8) | 26 (50.0) |
| TT | 15 (11.6) | 16 (11.7) | 5 (11.9) | 6 (11.5) |
| p Value<sup>a</sup> | 0.97571 | | 0.82901 | |
| C allele | 167 (64.7) | 179 (65.3) | 51 (60.7) | 66 (63.5) |
| T allele | 91 (35.3) | 95 (34.7) | 33 (39.3) | 38 (36.5) |
| p Value<sup>b</sup> | 0.88472 | | 0.69928 | |
| c.597C>T/rs229107 | | | | |
| CC | 49 (38.0) | 51 (37.2) | 12 (28.6) | 15 (28.8) |
| CT | 57 (44.2) | 60 (43.8) | 22 (52.4) | 27 (51.9) |
| TT | 23 (17.8) | 26 (19.0) | 8 (19.0) | 10 (19.2) |
| p Value<sup>a</sup> | 0.97042 | | 0.99902 | |
| C allele | 103 (39.9) | 112 (40.9) | 38 (45.2) | 47 (45.2) |
| T allele | 155 (60.1) | 162 (59.1) | 46 (54.8) | 57 (54.8) |
| p Value<sup>b</sup> | 0.82278 | | 0.99500 | |
| c.1086C>T/rs57040246 | | | | |
| CC | 129 (100.0) | 137 (100.0) | 42 (100.0) | 52 (100.0) |
| CT | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| TT | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| T allele | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| c.1463G>C/rs59502379 | | | | |
| CC | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| CG | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| GG | 129 (100.0) | 137 (100.0) | 42 (100.0) | 52 (100.0) |
| C allele | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| p Value<sup>a</sup> | 0.66841 | | 0.41932 | |
All SNPs, except c.1463G>C and c.1086C>T, occurred at an allele frequency higher than 12.0%. Variant alleles of SLCOB1 c.1463G>C and c.1086C>T polymorphisms were not identified in either ethnic group in this study. The frequency of the c.521T>C SNP was the lowest, 13.7 and 12.2% for Macedonians and Albanians, respectively, while the frequencies of all other SNPs alleles were above 40.0%, with frequency of the c.571T>C variant allele being highest in both populations (65.0 and 62.2% for Macedonians and Albanians, respectively). No significant differences (p >0.05) in allelic frequencies and genotype distributions of the analyzed SNPs were observed between the two ethnic groups. The SNP variant allele frequencies in the ethnic groups separately compared to data reported from various ethnic populations. The variant allele frequencies between females and males within the ethnic group.

Pairwise Linkage Disequilibrium. Pairwise LD profiles for single SNPs using $r^2$ and $D'$ values for Macedonians and Albanians separately, are shown in Figures 1 and 2, respectively. Generally, the correlations of SNP pairs in the Albanian population were weaker than those of the Macedonian population. The most strongly correlated ($r^2 \geq 0.33$) SNP pair in the Macedonian population was c.597C>T/c.388A>G ($r^2 = 0.531, D' = 0.740$), followed by c.597C>T/c.*439T>G ($r^2 = 0.373, D' = 0.699$). Other pairs showing a significant association were c.388A>G/c.*439T>G ($r^2 = 0.289, D' = 0.613$) and c.521T>C/m.571T>C ($r^2 = 0.233, D' = 0.919$). The correlation of the most common SNP pair, c.388A>G/c.521T>C, in the Macedonians was relatively weaker compared to other SNP pairs, with $r^2 = 0.113$ and $D' = 0.698$. The c.521T>C showed the strongest correlation of this SNP with c.571T>C ($r^2 = 0.746$), c.388A>G and c.*439T>G ($r^2 = 0.221, D' = 0.498$ and $r^2 = 0.214, D' = 0.505$, respectively. The correlation between c.388 A>G and c.521T>C in the Albanian population was weaker ($r^2 = 0.097, D' = 0.219$) compared to the same SNP pairs in the Macedonian population. Similar data for the LD of c.521T>C with other SNPs were obtained, with the strongest correlation of this SNP with c.571T>C ($r^2 = 0.091, D' = 0.635$), followed by c.597C>T ($r^2 = 0.097, D' = 0.746$), c.388A>G and c.*439T>G ($r^2 = 0.008, D' = 0.238$).

Haplotypes. The haplotype analysis revealed 20 different haplotypes in the Macedonian population and 21 in the Albanian population (Tables 5 and 6). Nine haplotypes in each of the two populations were designated as new. Nine other haplotypes that occurred in the Macedonian and Albanian populations had the same sequence of the actually investigated SNPs as in the newly identified haplotypes presented in the study of Pasanen et al. [13].

In the Macedonian population, eight haplotypes occurred at a frequency equal to or greater than 3.0% (Table 5). The most common haplotype in this ethnic group, *1J/*1K/*1L, had a frequency of 39.0%, containing variant allele C at position c.571 and having referent nucleotides at all other investigated positions. The variant allele C at position c.571 existed in eight haplotypes, with a frequency between 0.3 and 39.0%. The variant allele G at position c.388 and T at c.597C>T SNP existed in 11, while the variant allele G at c.*439T>G in 12 haplotypes, all occurring with frequencies between 0.3 and 11.6%. The c.521T>C SNP existed in six haplotypes, with a frequency between 0.3 and 8.6%. The variant alleles of the functionally most distinguished SNPs, c.388A>G
| Ethnic Group          | n | c.388A>G | c.521T>C | c.571T>C | c.597C>T | c.1086C>T | c.1463G>C | c.439T>G | p Value<sup>a</sup> | p Value<sup>b</sup> | Refs. |
|----------------------|---|----------|----------|----------|----------|-----------|-----------|----------|-------------------|-------------------|--------|
| American (African)   | 22 | 0.75     | 0.023    | 0.045    | –        | –         | 0.09      | –        | <0.00001          | <0.00001          | 12     |
| (European)           | 49 | 0.30     | 0.14     | 0.53     | –        | –         | 0.00      | –        | 0.812508          | 0.675274          | 12     |
| (Native)             | 64 | 0.63     | 0.24     | 0.33     | 0.28     | 0.01      | 0.005     | 0.041    | 0.000507          | 0.003258          | 11     |
| European (Caucasian) | 151| 0.41     | 0.18     | 0.61     | 0.42     | 0.00      | 0.30      | 0.118756 | 0.149653          | 11     |
| Sub-Saharan African  | 105| 0.79     | 0.019    | 0.13     | 0.50     | 0.07      | 0.67      | <0.00001 | <0.00001          | 11     |
| Oceanian             | 28 | 0.66     | 0.00     | 0.48     | 0.52     | 0.036     | 0.00      | 0.30     | 0.017744          | 0.055677          | 11     |
| Algerian             | 29 | 0.64     | 0.17     | 0.21     | 0.59     | 0.017     | 0.00      | 0.72     | 0.004001          | 0.017564          | 11     |
| Tunisian             | 115| 0.78     | 0.039    | 0.061    | 0.00     | 0.02      | –         | <0.00001 | <0.00001          | 11     |
| Indian (Asian)       | 35 | 0.60     | 0.071    | –        | 0.00     | –         | –         | –        | 0.078203          | 0.167511          | 24     |
| North Indian         | 100| 0.57     | 0.065    | 0.44     | 0.22     | 0.00      | –         | –        | 0.000100          | 0.009301          | 25     |
| Brazilian (African)  | 322| 0.25     | –        | 0.41     | 0.00     | –         | 0.00      | –        | 0.000000          | 0.000000          | 13     |
| (Mulatto)            | 603| 0.25     | –        | 0.41     | 0.00     | –         | 0.00      | –        | 0.000000          | 0.000000          | 13     |
| (Caucasian)          | 102| 0.79     | 0.019    | 0.13     | 0.50     | 0.07      | 0.67      | <0.00001 | <0.00001          | 11     |
| (Amerindian) Brazilian| 143| 0.26     | 0.14     | –        | 0.00     | –         | –         | –        | 0.164989          | 0.136491          | 19     |
| Chinese              | 178| 0.73     | 0.11     | 0.27     | 0.42     | 0.00      | 0.00      | 0.27     | <0.00001          | <0.00001          | 11     |
| Han Chinese          | 100| 0.80     | 0.13     | 0.26     | 0.50     | 0.00      | 0.27      | 0.124778 | 0.264367          | 24     |
| Uyghur (Chinese)     | 731| 0.62     | 0.10     | –        | –        | 0.00      | –         | –        | 0.000925          | 0.119961          | 40     |
| Finnish (Caucasian)  | 468| 0.46     | 0.20     | 0.53     | 0.46     | –         | –         | 0.49     | 0.038427          | 0.134013          | 13     |
| Dutch                | 74 | 0.18     | –        | –        | –        | –         | –         | –        | 0.797881          | 0.339359          | 29     |
| German (Caucasian)   | 300| 0.37     | 0.15     | 0.35     | 0.38     | –         | –         | 0.00     | 0.002137          | 0.078291          | 36     |
| Israeli              | 133| 0.46     | 0.20     | 0.56     | 0.45     | 0.00      | 0.00      | 0.55     | 0.322641          | 0.571025          | 11     |
| Japanese             | 120| 0.63     | 0.16     | 0.36     | 0.43     | –         | –         | –        | <0.00001          | 0.005088          | 34     |
| Korean               | 24 | 0.75     | 0.25     | –        | –        | –         | –         | –        | 0.775142          | 1.000000          | 35     |
| Malaysian            | 100| 0.87     | 0.11     | 0.24     | 0.50     | 0.00      | 0.00      | 0.47     | 0.023446          | 0.89754         | 36     |
| Pakistani            | 192| 0.47     | 0.09     | 0.56     | 0.26     | 0.00      | 0.00      | 0.59     | 0.008402          | 0.815183          | 11     |
| Tanzanian            | 366| 0.87     | 0.06     | –        | –        | –         | –         | –        | <0.00001          | 0.289424          | 38     |
| Turkish              | 94 | 0.46     | 0.12     | 0.38     | 0.36     | –         | 0.00      | –        | 0.89754           | 0.289424          | 36     |
| Albanian             | 266| 0.41     | 0.14     | 0.65     | 0.40     | 0.00      | 0.00      | 0.50     | 0.928464<sup>c</sup> | this study    | 13     |
| Greek                | 403| 0.43     | 0.16     | –        | –        | –         | –         | –        | 0.811389          | 0.593568          | 27     |
| Caucasian            | 423| 0.37     | 0.15     | –        | –        | –         | –         | –        | 0.472334          | 0.333625          | 32     |

<sup>a</sup> n: number of patients.

<sup>b</sup> The p value of differences in allele frequencies between Macedonians and different ethnic groups.

<sup>c</sup> The p value of differences in allele frequencies between Albanians and different ethnic groups.

<sup>d</sup> The p value of differences in allele frequencies between Albanians and Macedonians.
and c.521T>C, were present in four haplotypes, of which the dominant haplotype *15/*16/*17 had a frequency of 8.6%.

In the Albanian population, 10 haplotypes occurred at a frequency equal or greater than 3.0% (Table 6). The most common haplotype was the same as in the Macedonian ethnic group, *1J/*1K/*1L, with a frequency of 26.6%. The variant allele C at position c.571 existed in nine haplotypes with a frequency between 1.4 and 26.6%. The variant allele G at position c.388 existed in 10 haplotypes, while c.597C>T SNP in 11 haplotypes, both occurring at frequencies between 1.0 and 12.4%. The c.*439T>G occurred in 10 haplotypes, with a frequency between 0.6 and 12.4%, and the c.521T>C SNP existed in seven haplotypes, with a frequency between 0.6 and 3.7%. Three of the haplotypes contained the variant alleles of the c.388A>G and c.521 T>C SNPs with a frequency ≥1.0%, with the major haplotype *15/*16/*17 having a frequency of 2.4%.

**DISCUSSION**

It is clearly evident that the mutations in the **SLCO1B1** gene and their clinical significance for a large number of endogenous and xenobiotic substrates...
SNPs OF THE SLCO1B1 GENE

transported by OATP1B1 is a persistent motivation for scientific research. To the best of our knowledge, this is the first study in which polymorphisms contained in the SLCO1B1 gene were studied in the populations living in the Western Balkan Peninsula. For this reason, commonly seen mutations (c.388A>G, c.521T>C, c.571T>C, c.597C>T, c.*439 T>G) as well as coding region SNPs that were not identified in the Caucasian (European) population (c.1086C>T, c.1463G>C) were selected for genotyping. Our data confirmed that SLCO1B1 is highly polymorphic and that several variants appear at a high frequency, both in the Macedonian and Albanian populations. The SNPs c.388A>G (Asn130Asp), c.571T>C (Leu191Leu), c.597C>T (Phe199Phe) and c.*439T>G, all occurred with an allelic frequency between 40.0 and 65.0%. The non synonymous c.521T>C SNP, which has been constantly associated with a reduced OATP1B1 activity, was found with an allele frequency of approximately 14.0 and 12.0% in the Macedonian and Albanian population, respectively, which is nearly equal to that reported for Caucasians (15.0%) [32], slightly lower than that reported previously for Dutch (18.0%) [33], Finish (20.0%) [13],

| SLCO1B1 Haplotype | c.388 A>G | c.521 T>C | c.571 T>C | c.597 C>T | c.1086 G>C | c.1463 G>C | c.*439 T>G | Haplotypes Found |
|-------------------|----------|----------|----------|----------|----------|----------|----------|-----------------|
| Reference         | A        | T        | T        | C        | C        | G        | T        | % 95% CI        |
| *1J/*1K/*1L*      |          |          |          |          |          | G        | T        | 45 26.6 0.618-1.618 |
| *1G/*1H/New*      | G        | C        | T        |          |          |          |          | 21 12.4 0.525-1.905 |
| *1L/*1J/*1K*      |          |          | C        |          |          | G        | T        | 19 11.5 0.514-1.947 |
| *1A/*1F/New*      |          |          |          |          |          | G        | T        | 11 6.7 0.424-3.344 |
| *20/A/21/New*     | G        | C        | T        |          |          |          |          | 8 5.1 0.380-2.630 |
| *1B/*1P/New*      | G        | C        | T        |          |          |          |          | 6 3.8 0.330-0.301 |
| *25/New*          | C        | T        |          |          |          |          |          | 6 3.7 0.322-3.103 |
| New               |          |          |          |          |          | G        | T        | 6 3.5 0.316-3.162 |
| New               |          |          |          |          |          | C        | T        | 5 3.2 0.297-3.370 |
| New               |          |          |          |          |          | C        |          | 5 3.0 0.286-3.497 |
| New               |          |          | C        | C        | T        |          |          | 4 2.9 0.280-3.573 |
| New               |          |          | C        | C        | T        |          |          | 4 2.7 0.268-3.734 |
| New               |          |          |          |          |          | G        | T        | 4 2.5 0.259-3.865 |
| New               |          |          | G        |        |        |          |          | 4 2.4 0.251-3.990 |
| New               |          |          |          |          |          | C        | T        | 3 2.2 0.236-2.436 |
| New               |          |          |          |          |          | G        | T        | 3 1.9 0.212-4.716 |
| New               |          |          |          |          |          | C        | T        | 3 1.9 0.210-4.755 |
| New               |          |          |          |          |          | G        | T        | 2 1.4 0.168-5.938 |
| New               |          |          |          |          |          | C        | T        | 1 1.0 0.114-8.806 |
| New               |          |          |          |          |          | G        | T        | 1 0.7 0.082-12.179 |
| New               |          |          |          |          |          | C        |        | 1 0.6 0.065-15.451 |

95% CI: 95% confidence interval.

* The name includes the presented sequence of the SNPs investigated in this study and referent alleles of the additional SNPs investigated in the study by Pasanen et al. [13].

** The haplotype name includes a sequence of the SNPs investigated in this study and referent alleles in other SNPs investigated in the cited study [13], except at the following positions: b: c.411 and c.463; h: g.-11110; i: c.1929; j: g.-11187 and c.1929; k: g.-10499; and l: g.-11187, where variant alleles exist.

*** The haplotype is assigned as new by Pasanen et al. [13], having the same sequence of the SNPs investigated in this study and referent alleles in other SNPs investigated in the cited study, except at the following positions: c: g.-11110, c.411 and c.463; f: g.-11187; and g: g.-10499, where variant alleles exist.

**** The haplotype is assigned as new by Pasanen et al. [13], having the same sequence of the SNPs investigated in this study and referent alleles at additional SNPs investigated in the cited study (at positions g.-11187, g.-11110, g.-10499, c.411, c.463 and c.1929).
Algerian (17.0%) [11], Israeli (20.0%) [11], Japanese (16.0-19.0%) [11,34] and Korean (25.0%) [35] ethnic groups, and much higher than that reported for African Americans (2.3%) [12] and Sub-Saharan Africans (1.9%) [11] (Table 4). So far, literature data point to equal allele frequency for this SNP in Macedonians and European Americans [12] and Han Chinese [29], although a lower number of subjects in the last two groups was included in the study. The same was observed in Albanian and Turkish subjects, with an equal number of subjects in the study [36]. Compared to studies with Native Americans, Caucasian Europeans, Sub-Saharan Africans, Japanese and Israeli subjects [11], the variant alleles found in the Macedonian and Albanian subjects were lower for c.388A>G (41.0-42.0% vs. 46.0-79.0%), higher for c.571T>C (62.0-65.0% vs. 13.0-61.0%) and nearly equal for c.597C>T (40.0-45.0% vs. 42.0-50.0%), with the exception of Native Americans in which a much lower allele frequency was observed (28.0%). The allele frequency for SNP c.*439T>G was lower in comparison with Sub-Saharan Africans (47.0-50.0% vs. 76.0%), higher than that of Caucasian Europeans (30.0%) and almost equal to the frequency of other ethnic groups, where a variant G allele existed with a frequency between 41.0% (Native Americans) and 55.0% (Israeli) (Table 4). No variant alleles were found for c.1086C>T and c.1463G>C SNPs in the Macedonian and Albanian populations and the same was observed in German, Finish, Japanese, Israeli and Turkish subjects [11,36], while in the studied Native American and Sub-Saharan African, Ugandan and Pakistani ethnic groups, a low frequency of variant alleles was observed, between 1.0 and 7.0% for vari-
SNPs OF THE SLCO1B1 GENE

For all SNPs, the distributions of the genotypes did not differ significantly ($p > 0.05$) between healthy subjects and patients and between male and female subjects. These data are partly in accordance with the results obtained in the study of Hubacek et al. [37], in which no difference for genotype distributions of rs4149056 variant between male and female subjects was observed. However, the results of the same study pointed to possible gender-dependent effects of this SNP within the SLCO1B1 gene on statin treatment efficacy.

It is increasingly evident that the most relevant variants, the SNPs 388A>G and 521T>C, have a major effect on OATP1B1 activity. However, their association and other SNPs in LD with these functionalities may modify the respective phenotype and explain the discrepant effects of some SNPs on OATP1B1 activity in vivo. Most of the literature data point to a strong association between this SNP pair and its effect on drug response [20,29]. In the actual study, the association between c.388A>G and c.521 T>C was relatively weaker compared to other SNP pairs, especially those in the Albanian population. These data and generally, the differences between the two populations in LD data, are probably explained by the significantly smaller number of Albanian subjects included in the study and random sampling variation. The c.521T>C SNP showed the strongest correlation with the c.597C>T in both populations and the similar results have been obtained in the study of Pasanen et al. [13], in which a large sample (468) of Caucasian subjects was included.
Compared with the analysis performed with single SNPs, haplotypes often better predict the associated phenotype. In the present study, the most common SLCO1B1 haplotype, *II/*IK/*IL, contained the synonymous c.571 T>C SNP as compared with the reference sequence. It occurred at a frequency (35.6%) similar to that reported in the study of Pasanen et al. [13]. The c.521T>C SNP existed in two (*5 and *15/*16/*17) major haplotypes in the Macedonian and Albanian populations and one new, identified in the Albanian population only. Both common haplotypes, with a frequency of 2.0 and 3.7% (for *5) and 2.4 and 8.6% (for *15/*16/*17) in the Macedonian and Albanian subjects, respectively, contained the c.597C>T and c.439T>G SNPs. In the new haplotype identified in the Albanian population, instead of variant G allele in the c.439T>G SNP, variant C allele of c.571T>C existed, with referent alleles in other SNPs. Considering the significantly smaller number of subjects in the Albanian population, as potential limitation of this study, this result should be confirmed in a study in which a larger number of Albanian subjects would be included. The frequencies of the major haplotype *15/*16/*17 containing the variant alleles of the functionally most significant SNP pair c.388A>G/ c.521T>C (8.6 and 2.4% for Macedonians and Albanians, respectively) were lower than the frequency of haplotype *15 reported for Chinese (14.0%) and Japanese (15.8%), higher for Macedonians and comparable for Albanians with that of Caucasians (2.4%) and significantly higher than the one of African Americans (0.0%) [13,29].

In conclusion, this study presents an extensive analysis of SLCO1B1 variant genotype and haplotype distribution in selected populations living in the Western Balkan Peninsula, Macedonians and Albanians for the first time. No significant differences (p >0.05) in allelic frequencies and genotype distributions of the analyzed SNPs were observed between the two ethnic groups and the data are similar to those for Caucasians. About 8.6 and 2.4% of the Macedonians and Albanians, respectively, carrying the SLCO1B1*15 or SLCO1B1*16 or SLCO1B1*17 variant may exhibit altered/impaired transport activity of OATP1B1.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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