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Frequency of Single Nucleotide Polymorphisms of the *SLCO1B1* Gene in Slavic Population of Central Europe

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Abstract: The organic anion transporting polypeptide 1B1 (encoded by *SLCO1B1* gene) is involved in the active cellular influx of diverse endogenous compounds and several drugs, such as HMG-CoA reductase inhibitors (statins). Two common polymorphisms c.388A>G and c.521T>C in *SLCO1B1* alter transport activity of this transporter and play an important role in the pharmaceutical response to many drugs. The aim of our study was to investigate frequencies of common SNPs in *SLCO1B1* gene in Western Slavic population. We determined frequencies of two common polymorphisms c.388A>G and c.521T>C in the *SLCO1B1* gene in the control group consisting of 83 healthy volunteers from Slavic population by PCR-RFLP and allele-specific Real-Time PCR. Presented results were statistically evaluated and compared with known data of different ethnic groups. The allelic frequencies of *SLCO1B1* SNPs were 37% for minor allele c.388G and 23% for c.521C. *SLCO1B1* SNPs c.388A>G and c.521T>C were relatively frequent in Slovak population and allelic frequencies generally correspond with data published for other population of Caucasian origin. We also determined that 19% of individuals with Gilbert syndrome (ATA7/7TAA) carried the genotype c.388GG of the *SLCO1B1* gene. According to our findings, analyzed SNPs in the *SLCO1B1* gene are frequent enough for consideration of their screening in patients indicated for treatment with drugs involved in OATP1B1 mediated transport. Detection of polymorphisms in *SLCO1B1* is beneficial for avoiding adverse drug reaction.

Keywords: *SLCO1B1*, Statin, c.521T>C, c.388A>G, Pharmacogenetics

Introduction

Organic Anion Transporting Polypeptides (OATPs) represent family of proteins, which participate in the membrane transport of endogenous and xenobiotic compounds. OATPs are expressed in many types of tissues, including the liver, lung, heart, kidney, brain, intestine, placenta, testes (Hagenbuch and Meier, 2003).

The organic anion transporting polypeptide 1B1 (encoded by *SLCO1B1* gene) is one of the main hepatic uptake transporters, which is localized on the basolateral part of hepatocytes. It is involved in active cellular influx of diverse endogenous substrate, such as bile acids, bilirubin, conjugates of steroid hormone and drugs-HMG-CoA reductase inhibitors, fexofenadine, rifampicin, bosentan, valsartan, temocaprilat and irinotecan metabolite SN-38 (Chung *et al*., 2005; Pasanen *et al*., 2006a; Cvetkovic *et al*., 2009; Nishizato *et al*., 2003; Xiang *et al*., 2009; Treiber *et al*., 2007; Maeda *et al*., 2006). Changes in the activity of this transporter play an important role in pharmaceutical response to many drugs (Niemi *et al*., 2004).

The *SLCO1B1* gene is located on the short arm of a chromosome 12 and spans fifteen exons. It encodes protein of 691 amino acids with 12 transmembrane helices. A lot of allelic variants of *SLCO1B1* gene were identified in the past, 190 common variants have minor allele frequency greater than 5% (http://hapmap.ncbi.nlm.nih.gov/). Interesting for genetic study are c.388A>G (rs2306283) and c. 521T>C (rs4149056) polymorphisms that resulted in the definition of *SLCO1B1*B* and *SLCO1B1*5* respectively

(Nishizato *et al*., 2003; Tirona *et al*., 2001). At the variant c.388A>G (N130D), the wild-type A allele encodes asparagine while the minor G allele encodes aspartic acid, at variant c.521T>C (V174A), the wild-type T allele encodes valine while the minor C allele encodes alanine. These substitutions are associated with altered transport activity of OATP1B1 (Tirona *et al*., 2001; Nies *et al*., 2013). Biochemically important feature of these polymorphisms may be impact on elevation of blood bilirubin concentration and *SLCO1B1* SNPs could be further possible factor for the induction of hyperbilirubinemia (Huang *et al*., 2004; 2005). Subsequent unfavorable effect of these polymorphisms is based on their linkage with statin-induced myopathy. Association between risk of statin-induced myopathy and variant in the *SLCO1B1* gene was described by SEARCH study group (GWAS) in 2008 (Link *et al*., 2008). This association was also identified in next studies (Voora *et al*., 2009; Brunham *et al*., 2012; Donnelly *et al*., 2011; Carr *et al*., 2013). These findings revealed that *SLCO1B1* genotyping can be used to guide choice and/or dose of statin therapy with the goal of reducing the risk of muscle impairment and optimization of adherence to the therapy (Stewart, 2013). Guideline for simvastatin treatment considering *SLCO1B1* genotype was suggested by Wilke *et al*. (2012).

The frequency of c.388A>G and c.521T>C varies significantly between different populations worldwide. The c.388A>G SNP allele frequency was observed 30-45% in Caucasians, 70-80% in African populations and 60-90% in Asian populations. The c.521T>C SNP allele frequency was found out to be 10-20% in European, 10-15% in Asian populations and 1-4% in African population (Tirona *et al*., 2001; Jada *et al*., 2007; Mwinyi *et al*., 2008).

Different frequencies in various populations indicate, that pharmacogenetic-testing for these variants is dependent on a particular population genetic architecture. For this purpose, it is important to characterize *SLCO1B1* genetic variation in different populations. To the best of our knowledge, the study about incidence of *SLCO1B1* polymorphisms in Slovak population, has not been published yet. The aim of our study was to analyze *SLCO1B1* SNPs gene in Slovak population, to identify frequency and compare our findings with other populations. Whereas polymorphisms in *SLCO1B1* gene have impact on bilirubin level, the second aim was to detect incidence of *SLCO1B1* SNPs in probands with Gilbert syndrome, characterized by presence of (TA)7 tandem repeat of promoter (TATA box) *UGT1A1* gene. In this group we suppose a cumulative genetic effect on hyperbilirubinemia due to influence of both genetic factors on bilirubin metabolism. This study provides valuable information about genetic variability *SLCO1B1* gene in Western Slavic population.

Materials and Methods

Sample

Control group consisted of 83 healthy unrelated subjects 166 alleles from Slovak inhabitants of Slavic origin (48 men and 35 women). All participants signed a written informed consent before entering the study. They were randomly selected from available database of healthy volunteer samples. The data for BMI, clinical and biochemical parameters and the age was also collected, but these data are not relevant for the present study.

Sample Preparation

Blood samples for DNA extraction were collected in 3 mL tubes containing potassium EDTA. DNA was isolated from leukocytes using MN NucleoSpin Blood mini (Macherey-Nagel).

Genotyping

Isolated DNA was screened for two *SLCO1B1* polymorphisms c.388A>G and c.521T>C.

Polymorphism c.388A>G was detected by PCR-RFLP using primers published by Mwinyi *et al.* (2008). The PCR amplification was performed in a PCR thermal cycler and consisted of initial denaturation of 5 minutes at 95°C followed by 35 cycles of denaturation for 30 sec at 95°C, annealing for 30 sec at 51°C, extension for 30 sec at 72°C and a final extension for 10 min at 72°C. PCR product was digested with the appropriate restriction enzyme ClaI. Change from A to G creates restriction site for ClaI following 274 bp PCR fragment cleaves to 155 and 119 bp fragment (Mwinyi *et al*., 2008). RFLP fragment was analyzed on a 2% agarose gel.

Polymorphism c.521T>C (rs4149056) was analyzed by TaqMan SNP genotyping Assay C_30633906_10 (Applied Biosystems).

Polymorphism in promotor region of UGT1A1-ATA7/7TAA was detected by fragment analysis by capillary electrophoresis in genetic analyzer ABI310. Primers GS1-1: TAACTTGGTGTATCGATTGGTTTTTG and GS1-2: ROX-ACAGCCATGGCGCCTTTGCT were used for amplification of promotor region of *UGT1A1* gene.

Statistical Analysis

The Hardy-Weinberg test was applied to confirm the independent segregation of the alleles of individual genotypes. Fisher's exact test was used for the analysis of differences between populations. Data were analyzed with statistical online software CubeX (Gaunt *et al*.,

2007) (haplotype analysis, linkage disequilibrium, Hardy-Weinberg test, Chi-square test) and SPSS software (Fisher exact test). The p-value of less than 0.05 was accepted as significant ($p<0.05$).

Results

83 healthy volunteers (166 alleles) from Slovak population were analyzed for 2 polymorphisms in the *SLCO1B1* gene and for polymorphism A(TA)6/7TAA in the promotor region the *UGT1A1* gene. PCR-RFLP was used to detect polymorphism c.388A>G (Fig. 1) and allele-specific Real-Time PCR analysis for c.521T>C (Fig. 2a-c) in the *SLCO1B1* gene.

The results of our study are shown in Table 1. The frequency of studied polymorphisms is similar to frequency observed in majority of Europe's population. The occurrence of the minor allele (G) of the polymorphism c.388A>G was 37% and 13% of studied subjects carried genotype c.388GG. 521C allele occurrence was 23% and only 5% of individuals carried genotype c.521CC. We compared acquired results (Table 1) with allelic frequencies from different ethnic populations (Table 2).

Table 1. Allelic and genotype frequencies of *SLCO1B1* SNPs in Slovak population

SNP	Allele	Frequency (%)	Genotype	Frequency (%)
c.388A>G	A	63	AA	40
	G	37	AG	47
			GG	13
c.521T>C	T	77	TT	58
	C	23	TC	37
			CC	5

Table 2. *SLCO1B1* SNPs allelic frequencies in different populations (‡ significant differences between Slovak and other populations, $p<0.05$

Population	Number	c.388A>G	p value[a]	c.521T>C	p value[b]	Refs.
Slovak	83	37 (29.4-44.6)*		23 (17,3-30,7)*		Current study
German	300	36,5	1.000	15‡	0.019	(Mwinyi *et al*., 2008)
Hungarian	442	36.2	0.930	18,9	0.241	(Nagy *et al*., 2015)
Roma	470	54,5‡	0.000	17,2	0.100	(Nagy *et al*., 2015)
Turkish	94	46,3	0.084	12,2‡	0.011	(Mwinyi *et al*., 2008)
White Canadian	41	50	0.055	18,3	0.510	(Boivin *et al*., 2010)
African	115	77,8‡	0.000	3,9‡	0.000	(Mwinyi *et al*., 2008)
European American	49	30,6	0.349	14,3	0.109	(Tirona *et al*., 2001)
African American	22	75,0‡	0.000	2,3‡	0.001	(Tirona *et al*., 2001)
Japanese	120	62.9‡	0.000	15,8	0.092	(Nishizato *et al*., 2003)
Finnish	468	46,2‡	0.028	20,2	0.466	(Pasanen *et al*., 2006b)
Chinese	111	73,4‡	0.000	14,0‡	0.031	(Xu *et al*., 2007)
Pakistani	180	50‡	0.005	23,9	0.826	(Rajput *et al*., 2014)
Malaysian	100	87‡	0.000	11‡	0.003	(Jada *et al*., 2007)
Indian	100	57‡	0.000	6,5‡	0.000	(Jada *et al*., 2007)
Tanzanian	366	87‡	0.000	6‡	0.000	(Aklillu *et al*., 2011)
Macedonian	266	40.9	0.364	13.7‡	0.008	(Grapci *et al*., 2015)
Albanian	94	42	0.328	12.2‡	0.011	(Grapci *et al*., 2015)
Greek	403	43	0.143	16‡	0.041	(Giannakopoulou *et al*., 2014)
European	151	41	0.375	18	0.224	(Pasanen *et al*., 2008)
Oceanian	28	66‡	0.000	0‡	0.000	(Pasanen *et al*., 2008)
Ugandan	115	78	0.000	3.9‡	0.000	(Pasanen *et al*., 2008)
Dutch	74	-	-	18	0.331	(Brunham *et al*., 2012)
Israeli	133	46	0.072	20	0.469	(Pasanen *et al*., 2008)
Korean	24	75‡	0.000	25	0.847	(Chung *et al*., 2005)
Algerian	29	64‡	0.000	17	0.458	(Pasanen *et al*., 2008)
Brazilian	143	26‡	0.019	14‡	0.020	(Santos *et al*., 2012)
Russian	1071	-	-	22	0.770	(Sychev *et al*., 2016)
Sakha (Russian)	76	-	-	11‡	0.007	(Sychev *et al*., 2016)

[a]The p value of the differences in allelic frequencies between Slovak and other population for c.388A>G
[b]The p value of the differences in allelic frequencies between Slovak and other population for c.521T>C
*95%CI: 95% Confidence interval

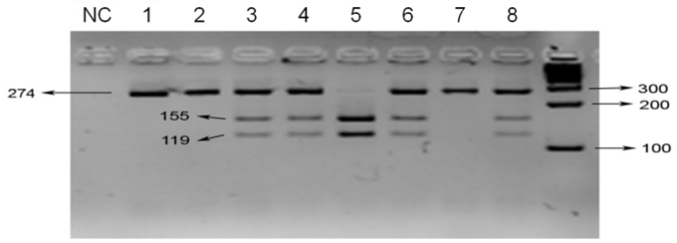
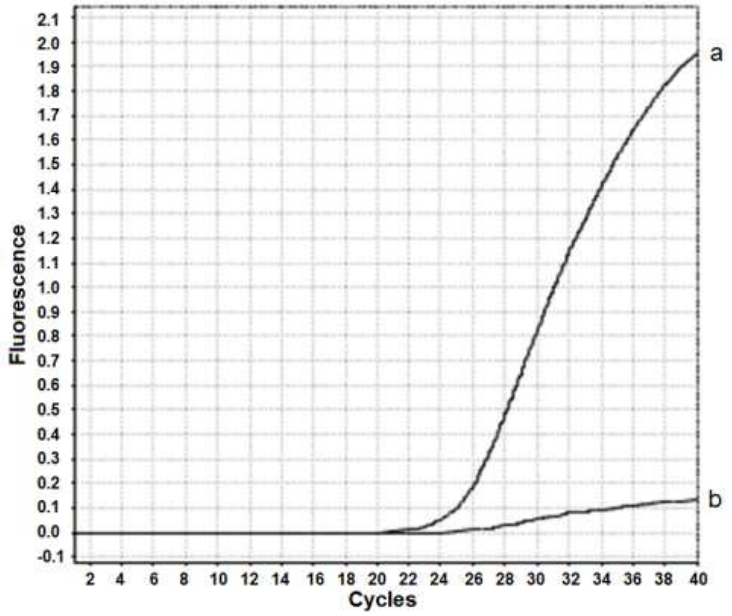
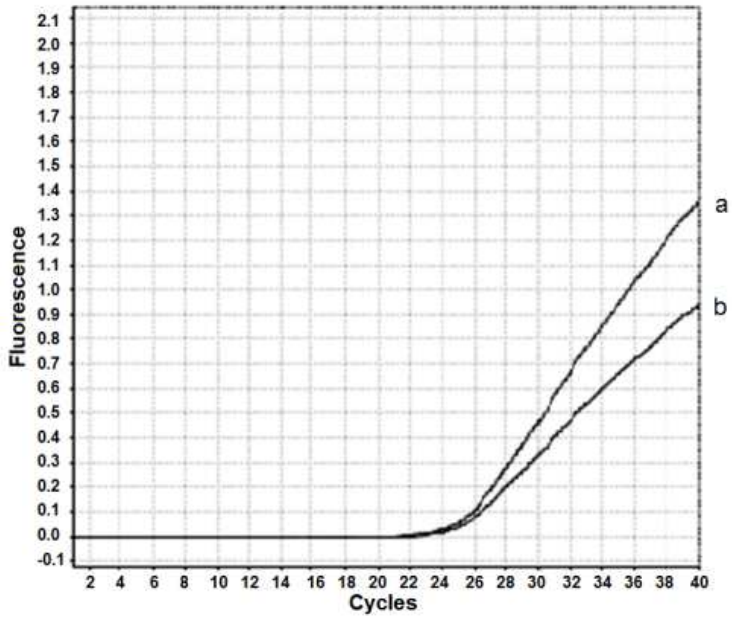


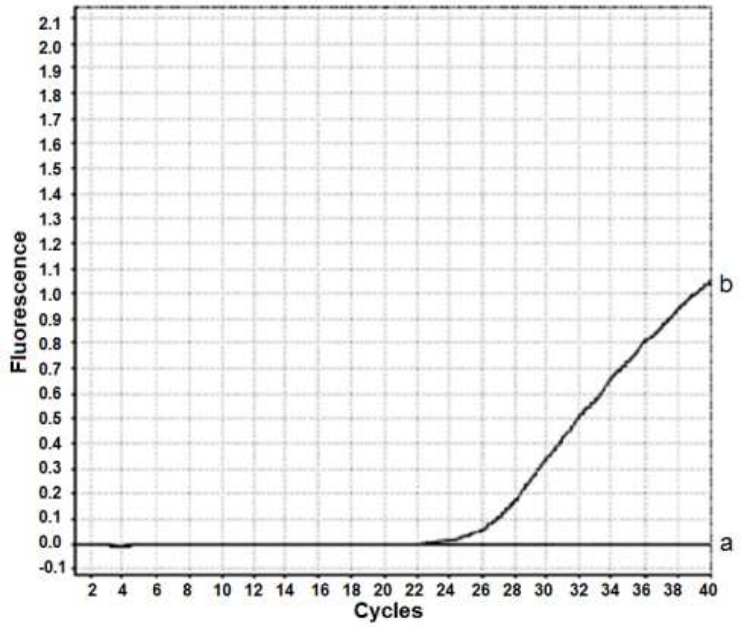
Fig. 1. PCR-RFLP analysis result for polymorphism 388A>G. Lane 1,2 and 7-wild type (AA), lane 3,4,6 and 8-heterozygotes (AG) lane 5 - homozygote for polymorphism 388A>G (GG)



(a)



(b)



(c)

Fig. 2. Schematic pictures Allele-specific Real-Time PCR analysis for polymorphism c.521T>C. 2a- wild type (TT), 2b- heterozygote (TC), 2c- mutant (CC); a- wild type allele, b- mutant allele

Table 3. Genotype frequencies of *SLCO1B1* SNPs in subgroups of promoter region TATA box in *UGT1A1* gene

SNPs *SLCO1B1*	c.388A>G				c.521T>C		
TATA genotype of *UGT1A1*	n	AA (%)	AG (%)	GG (%)	TT (%)	TC (%)	CC (%)
(TA)6/(TA)6	29 (35%)	15	18	2	18	16	1
(TA)6/(TA)7	38 (46%)	18	21	7	30	11	4
(TA)7/(TA)7	16 (19%)	7	8	4	10	10	0

Correlation between studied SNP pairs was tested by pairwise linkage disequilibrium. The value was r^2 = 0, 18 and D' = 0, 58, this means that these polymorphisms are co-inherited for 58%. The allelic frequencies at each locus were in Hardy-Weinberg equilibrium. In our study we found occurrence of all possible haplotypes for polymorphism c.388A>G and c. 521T>C with frequency for A-T (*SLCO1B1*1A*) 57%, A-C (*SLCO1B1*5*) 6,3%, G-T (*SLCO1B1*1B*) 19, 6% and G-C (*SLCO1B1*15*) 17, 1%.

The frequency of causal mutation for Gilbert syndrome (TA7/TA7) was 19% in the studied cohort. Three subjects of this group (TA7/TA7) carried mutant genotype c.388GG in *SLCO1B1* gene, which is 19% of individual with Gilbert syndrome (Table 3). These polymorphisms are not linked.

Discussion

Product of the gene *SLCO1B1* plays important role in the transport of numerous endogenous and exogenous compounds from blood into the liver cells. Polymorphisms c.521T>C and c.388A>G decrease transport activity of the OATP1B1. These non-synonymous substitutions have impact on the drug entry into the hepatocytes and increased drug plasma levels and therefore they modulate drugs therapeutic effects and enhance its toxicity. c.521T>C polymorphism causes decreased clearance of pravastatin, simvastatin, ezetimibe glucuronide, SN-38 and bilirubin (Oswald *et al*., 2008; Zhang *et al*., 2007; Nozawa *et al*., 2005; Neuvonen *et al*., 2008). Polymorphisms in *SLCO1B1* can be a further factor for hyperbilirubinemia and may be linked with Gilbert syndrome, as OATP1B1 is capable of transporting unconjugated bilirubin. However, the main factor for Gilbert syndrome is homozygous mutations in the promotor of bilirubin UDP-glucuronosyltransferase gene (Huang *et al*., 2004; 2005; Zhang *et al*., 2007). In the studied group with Gilbert syndrome, we found out 19% frequency of individuals carrying genotype c.388GG. In these subjects the risk of hyperbilirubinemia can be increased due to combined genetic factors. Because of low incidence of the genotype c.521CC we do not

consider it to play part on unconjugated hyperbilirubinemia in the group of patients with Gilbert syndrome. Substantial health problem concerning this topic is relationship between *SLCO1B1* SNPs and statin-induced myopathy, which has been noted in many studies. Statins are generally considered as safe and well-tolerated drugs, though, some users developed mild muscle impairment and in rare cases life-threatening rhabdomyolysis. Pasanen *et al*. (2006a) determined that homozygotes for 521C allele had higher plasma exposure to the active simvastatin acid than homozygotes for the wild T allele. However, recent study found no effect of c.521T>C on the risk of statin-associated myopathy in dyslipidemic patients treated with low statin doses (Hubáček *et al*., 2015). The genotype c.388GG was associated with lower risk of myopathy (Link *et al*., 2008). In addition, c.388GG genotype causes significant increase in atorvastatin response (reduction of LDL cholesterol) and may be important marker for predicting efficiency of lipid-lowering therapy (Rodrigues *et al*., 2011). Heterozygous carriers of *SLCO1B1*15* (388G, 521C) showed significantly higher plasma levels for pravastatin and pitavastatin compared to *SLCO1B1* wild type carriers (Chung *et al*., 2005; Nishizato *et al*., 2003; Niemi *et al*., 2004). Discrepancy of data concerning the impact of statin therapy on myopathy is probably determined by the variety of therapeutic doses and/or type of statins. In 2012 guidelines for simvastatin treatment were suggested, in 2014 was this guideline updated and supplemented by short review about *SLCO1B1* genotype and risk of myopathy for other statins. Lower dose of simvastatin or change type of statin in patient with 521C allele is recommended (Ramsey *et al*., 2014).

To the best of our knowledge, the current study is the first to show the frequencies of polymorphisms *SLCO1B1* gene in Slovak population, which represents Western Slavic population. We analyzed *SLCO1B1* SNPs in studied group to find out frequencies *SLCO1B1* SNPs in Slovak population. We researched two common variants 521T>C (rs4149056) and 388A>G (rs2306283), which are in linkage disequilibrium (LD) and together form the four haplotypes *SLCO1B1*A* (388A, 521T), *SLCO1B1*1B* (388G, 521T) *SLCO1B1*5* (388A, 521C), *SLCO1B1*15* (388G, 521C). The correlations of these SNP pairs were relatively low in Slovak population r^2 = 0,18 and D' = 0,58.

We determined that the presence of minor allele c.388G was frequent (38%) and frequency of mutant genotype was 13%. On the other hand, the minor allele frequency of c.521C was almost half less (23%) than 388G allele. When comparing our data with published studies, the most often occurring SNP c.388A>G in our studied population had a similar allelic frequency in German (Mwinyi *et al*., 2008), Hungarian (Nagy *et al*., 2015), Macedonian, Albanian (Grapci *et al*., 2015) and Greek (Giannakopoulou *et al*., 2014) population. Frequency SNP c.388A>G observed in African (78%) (Mwinyi *et al*., 2008), Malaysian (87%) (Jada *et al*., 2007), Tanzanian (87%) (Aklillu *et al*., 2011), Korean (75%) (Chung *et al*., 2005) and Chinese (73,4%) (Xu *et al*., 2007) population was almost twice the frequency determined in our study. Higher incidence of SNP 388A>G was observed also in Japanese (64%) (Nishizato *et al*., 2003), Indian (57%) (Jada *et al*., 2007), Algerian (64%), Oceanian (66%) (Pasanen *et al*., 2008), Finnish (46,2%) (Pasanen *et al*., 2006b), Pakistani (50%) (Rajput *et al*., 2014) and Roma (Hungarian) (55%) (Nagy *et al*., 2015) population. Compared to Slovak population, we determined significantly lower frequency only in Brazilian population (Santos *et al*., 2012). The incidence of SNP c.521T>C in Slovak population (23%) was slightly higher than in compared population of Caucasian and non-Caucasian origin, except for Russian (Sychev *et al*., 2016), where a similar frequency (22%) was observed.

As we expected, the significantly different allele distribution for c.388A>G and c.521T>C was detected in African (Mwinyi *et al*., 2008), African American (Tirona *et al*., 2001), Chinese (Xu *et al*., 2007), Malaysian, Indian (Jada *et al*., 2007), Oceanian (Pasanen *et al*., 2008), Brazilian (Santos *et al*., 2012) and Tanzanian (Aklillu *et al*., 2011) population compared to Slovak population. These populations have different origin than Slovak population. We also found out difference in Macedonians, Albanians (Grapci *et al*., 2015), Greeks (Giannakopoulou *et al*., 2014) compare to Slovaks for c.521T>C. Macedonians belong to South Slavic ethnic group, Albanian and Greek have their origin in the Middle East. It was interesting to find statistically significant difference between Slovak and Finnish (Pasanen *et al*., 2006b) population for c.388A>G and between Slovak and German (Mwinyi *et al*, 2008) for c.521T>C, though all three ethnic populations belong to Caucasian population. The difference may be explained by higher genetic diversity of Europe population. Europe population is divided into several haplogroups. Slovak inhabitants have common ancestor with central and east Slavs. Finnish population belongs to Finno-Ugrian and origin of this population comes from Far East. Germans belong to Germanic ethnic group and they are genetically different than the Slavs.

We studied population variability between Slovak population and other countries. This study was done in sample of Caucasian origin, although Slovak population is not homogenous (substantial proportion of inhabitants are of Roma origin- for the future, it

would be suitable to study also this group. Whereas in the case of Hungarian population difference with Roma population has been found).

Our result confirmed the different incidence of *SLCO1B1* SNPs in different ethnic groups. This finding suggests, that the guideline for pharmacogenetic-testing should be designed with regards to population genetic structure.

Conclusion

Incidence of the most common *SLCO1B1* SNPs is relatively common in Slovak population. Our study shows that frequency of c.388A>G and c.521T>C in Slovak population generally correlates with Caucasian population. It was interesting to find lower incidence than Finish population for c.388A>G and higher incidence than German population for c.521T>C. *SLCO1B1* genotyping may have clinical utility for adjusting doses of statin therapy to reduce the risk of myopathy development. By *SLCO1B1* genotyping it is necessary to take into account to ethnic differences in *SLCO1B1* SNPs. In Slovak population, the frequency of *SLCO1B1* SNPs is sufficient for consideration of molecular-genetic screening of *SLCO1B1* SNPs in patients elected for treatment with drug involved in OATP1B1 mediated transport, mainly statin because of increased risk of myopathy.

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Author's Contributions

All author have read and given approval of the final manuscript version.

Mikulová Michaela: Administered the experiment and wrote the manuscript, designed the study, laboratory experiments and data analysis.

Kramarová Veronika: Has been involved in revising the manuscript critically for important intellectual content, has made substantial contributions to conception and design.

Chandoga Ján: Designed the experiment, interpreted results, has made substantial contributions to conception and design, and has been involved in drafting manuscript.

Ethics

This article contains unpublished results. The author declare no conflict of interest in this work.

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