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Frequency of the three most common polymorphisms in the *MDR1* gene in Slovak population

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The human multidrug resistance gene (*MDR1*) is encoding the transmembrane transporter P-glycoprotein (P-gp) which plays an important role in the efflux of various drugs and thus is potentially influencing the drug-treatment outcome. It has been indicated that the level of P-gp activity may be affected by the presence of single nucleotide polymorphisms (SNP) in the gene which led to the studies estimating *MDR1*-SNP frequencies in various populations. Here, we have investigated the occurrence of seven SNP in the *MDR1* gene for the first time in Slovak population using multiplex SNaPshot genotyping method. The allelic frequencies of the most common gene variants, i.e. 1236C>T, 2677G>T, 2677G>A and 3435C>T were estimated to be 42.5%, 43.5%, 2%, and 44.5%, respectively. We found that the most prevalent haplotype in Slovak population is 1236C-2677G-3435C occurring in 42.2% of individuals. Our preliminary data show that it is reasonable and feasible to utilize *MDR1* genotypes and haplotypes in Slovak patients, e.g. those with acute myeloid leukemia, in order to adjust the individual effective drug dosage and predict the patient's response to the treatment as well as the treatment outcome.

Key words: MDR1 gene, P-glycoprotein, polymorphisms, MDR1 haplotypes, Slovak population

The P-glycoprotein (P-gp) is a large transmembrane energy-dependent transporter with important role in drug efflux. P-gp was found to be expressed in most of blood-tissue barriers, liver, kidneys, intestine, blood-brain barrier, endothelium, placenta, ovaries, testes and salivary glands [1–3]. The substrate specificity of P-gp is surprisingly wide, including pharmacologically distinct agents, i.e. anticancer, antihypertensive agents, antiarrythmics, glucocorticoids, antiviral drugs, antibiotics, immunosuppressants, antidepressants, neuroleptics, antiepileptics, antiacids, opioids and others [3]. The tissue localization and the broad substrate specificity suggest the importance of P-gp in absorption, distribution and excretion of many drugs [4–6].

P-gp is encoded by the human multidrug resistance 1 (*MDR1*) gene which was localized on 7p21.1 chromosome, comprises of 28 exons [7] and gives rise to a 4.5 kb mRNA. The first systematic study on single nucleotide polymorphisms (SNP) in the gene revealed 15 different variants and also for the first time showed that SNP may affect expression levels and *in vivo* activity of the P-gp [8]. This finding stimulated the screening for other polymorphisms in the gene and studies on their manifestation on RNA and/or protein level. Today more than 100 SNP are known in the *MDR1* gene (http://www.ncbi.nlm.nih.gov/SNP/) but most of them are silent, occur at very low frequencies or are located in intronic sequences.

The three most frequent polymorphisms in Caucasian population are 1236C>T, 2677G>T/A, and 3435C>T [9]. The 3435C>T substitution was the first silent SNP in the *MDR1* gene for which the effect on the P-gp expression level has been demonstrated despite the fact that it is located at a wobble position and does not change the amino acid sequence. A significant inverse correlation of the 3435 SNP has been observed with the P-gp activity *in vivo*; the individuals homozygous for the T-allele had the high detectable digoxin concentration in comparison to homozygotes for the C-allele displaying the low level of drug [8]. The effect of the 3435C>T change has been confirmed also in subsequent studies in which it caused alteration in digoxin [10], fexofenadine [11, 12] and cyclosporine levels [13, 14]. The other silent SNP in position 1236 with the CC reference genotype has been associated with lower peak drug concentration and reduced drug exposure

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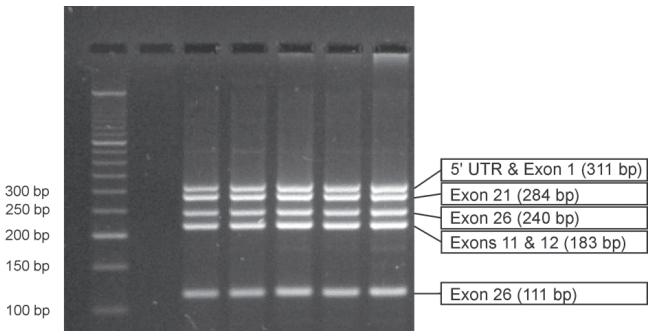

Figure 1. Multiplex PCRs of *MDR1* targets containing SNP. Five representative reactions products (10 µl) were resolved on a 25 g/l agarose gel stained with ethidium bromide.

when compared to the T allele carriers [15]. From the three most common polymorphisms the 2677C>T/A is the only one changing the protein primary structure and interestingly can result in two distinct amino acids, Ala893Ser (2677G>T) and Ala893Thr (2677G>A). It has been shown that the genotype variations had substrate-dependent effect in cellular system, affected the mRNA level and increased drug efflux [16, 17]. Published data also imply that this SNP may influence the time to relapse and overall survival from relapse/refractory disease in AML (Acute myeloid leukemia) patients [18, 19]. For the 3435 SNP contradictory results were found in different studies, some of them finding lower P-gp expression in 3435TT homozygotes, while other showing higher or no change in protein activity for the same genotype [3, 20–22].

Multiple studies have demonstrated that linkage disequilibrium exists between the 2677 and 3435 SNP suggesting that the haplotype evaluation might be better in predicting the functional effects. In agreement with this, several studies have already demonstrated that the pharmacokinetics predictions based on haplotype analysis are superior to the genotyping of individual SNP [22–24]. Subsequently, numbers of studies were dealing with evaluation of the *MDR1* genotype and haplotype frequencies in various populations using different genotyping techniques. In our study we analyzed *MDR1* gene polymorphisms and haplotypes in healthy subjects from Slovak population using SNaPshot Multiplex System with the aim to estimate the allelic and haplotype frequencies of this gene and compare the obtained data with other populations.

Table 1. Characteristics of the SNP analyzed in this study

SNP	Genomic location	dbSNP reference ID	Reference
-41A>G	Intron -1	rs2188524	[25]
-145C>G	Exon 1	rs34976462	[25]
-129T>C	Exon 1	rs3213619	[25]
1236C>T	Exon 11 & 12	rs1128503	[8]
2677G>T/A	Exon 21	rs2032582	[8]
3435C>T	Exon 26	rs1045642	[8]
4036A>G	Exon 28	rs3842	[25]

Materials and methods

Samples. Hundred unrelated healthy Slovak individuals were involved in this study. Genomic DNA was extracted from 200 µl of peripheral blood sample using QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany) following the manufacturer's protocol.

Multiplex PCR amplification of targets. Targets containing seven SNP listed in Table 1 were amplified in a five genomic segments (Figure 1) in a single multiplex PCR reaction using five pairs of primers (Table 2). Some of these primers were identical to those published previously [25]. The PCR reaction contained primers in a range from 0.15 µmol/l to 1.2 µmol/l, 12.5 µl of Multiplex PCR Master Mix (Qiagen, Hilden, Germany) and 100 ng DNA template in a final reaction volume of 25 µl. The reaction mixtures were subjected to initial denaturation at 94 °C for 15 min followed by 40 step-cycles of denaturation at 94 °C for 30 s, annealing at 56 °C for 30 s, extension at 72 °C for 1 min, and final extension at 72 °C for 5 min. The PCR products were purified by the enzymatic treatment with 10 U of Exonuclease I (Fermentas, Hanover, USA) and 1 U of SAP (Promega, Madison, USA) at 37 °C for 15 min and enzymes were subsequently inactivated at 80 °C for 15 min.

Single-base extension of SNP-specific primers. For the *MDR1*-SNP genotyping, we performed single base extension of 7 SNP-specific primers using ABI PRISM® SNaPshot® Multiplex Kit (Applied Biosystems, Foster City, USA). The SNP specific oligonucleotides (characterized in Table 3) were adopted from previously published study [25]. These primers consisted of a specific sequence (19–24 nucle-

Table 2. The primers used in the multiplex PCR of targets containing SNP

Region	5' - Primer	3' - Primer	Conc.[a]	bp[b]
5' UTR & Exon 1	5' - TCTACATAAGTTGAAATGTC - 3'	5' - AAACGAACAGCGGCCTCT - 3'	0.6	311
Exon 11 & 12	5' - ATTTAAACCTAGTGAACAGTC - 3'	5' - TCTCACCATCCCCTCTGT - 3'	0.3	183
Exon 21	5' - TGCAGGCTATAGGTTCCAGG - 3'	5' - TAGGGAGTAACAAAATAACAC - 3'	0.15	284
Exon 26	5' - TGAGAACATTGCCTATGGA - 3'	5' - CTTACATTAGGCAGTGAC - 3'	0.3	111
Exon 28	5' - CAGAATTATGAAGAGGTATC - 3'	5' - TACTTCTATAATCTTTTAGCAA - 3'	1.2	240

[a]final concentration of each primer in reaction mixture in µmol/l , [b]the length of PCR product

Table 3. The SNP-specific single-base extension primers used in SNaPshot

SNP	Location	Region	Primer sequence[a]	Conc.[b]	bp[c]
-41A>G	Intron -1	Promoter	5‘ - AACGCGCATCAGCTGAATCA - 3‘	0.15	20
-145C>G	Exon 1	Promoter	5‘ - act(gact)$_7$cTCTCTTTGCCACAGGAAG - 3‘	0.9	50
-129T>C	Exon 1	Promoter	5‘ - act(gact)$_3$gacGAGCTTGGAAGAGCCGCT - 3‘	0.025	36
1236C>T	Exon 11 & 12	NBD-1	5‘ - ct(gact)$_8$gACTCTGCATCTTCAGGTTCAG - 3‘	0.75	56
2677G>T/A	Exon 21	TM-9, 10	5‘ - t(gact)$_3$gacTTAGTTTGACTCACCTTCCCAG - 3‘	0.225	46
3435C>T	Exon 26	NBD2	5‘ - t(gact)$_{11}$gaCCTCCTTTGCTGCCCTCAC - 3‘	0.0125	66
4036A>G	Exon 26	3' UTR	5‘ - ct(gact)$_2$GACTTCATCAAGTGGAGAGAAATC - 3‘	0.05	30

[a]the low case letters represent nonhomologous tail at the 5' end of SNP primer, [b]final concentration of each primer in reaction mixture in µmol/l, [c]the length of the primer, NBD – nucleotide binding domain, TM – trans membrane domain, UTR – untranslated region

Table 4. The frequencies of *MDR1* SNP-genotypes in the Slovak population

Polymorphism	Location	Allele	Frequency	Genotype	Observed	Frequencies 95% CI	Expected
1236C>T	Exon 11& 12	C	57.5	CC	35	25.7-44.3	33.1
		T	42.5	CT	45	35.2-54.8	48.9
				TT	20	12.2-27.8	18
2677G>T/A	Exon 21	G	54.5	GG	32	22.9-41.1	29.7
		T	43.5	GT	43	33.3-52.7	47.4
		A	2	GA	2	0-4.7	2.2
				TA	2	0-4.7	1.7
				TT	21	13.0-29.0	18.9
				AA	-	-	-
3435C>T	Exon 26	C	55.5	CC	33	23.8-42.2	30.8
		T	44.5	CT	45	35.2-54.8	49.4
				TT	22	13.9-30.1	19.8

otides long) complementary to the analyzed region plus a poly(GACT) tail, which ensured spatial resolution of the extension products during capillary electrophoresis (final length of 20–66 nucleotides). The SNaPshot reactions contained SNaPshot Multiplex Ready Reaction Mix (2 µl), 7 SNP-specific primers (in final concentrations of 0.0125–0.9 µmol/l) and 2 µl of purified PCR products in a final reaction volume of 10 µl. The cycling program included 25 cycles of 96 °C for 10 s, 50 °C for 5 s, and 60 °C for 30 s. The extension products were purified by 15 min incubation with 1 U of SAP (Promega) at 37 °C and subsequent 15 min incubation at 80 °C to inactivate the enzyme. The purified SNaPshot products (0.5 µl) were mixed with 9 µl of Hi-Di™ formamide (Applied Biosystems) and 0.2 µl of GeneScan-120 LIZ Size Standard (Applied Biosystems), denatured and separated by capillary electrophoresis on ABI PRISM 310 Genetic Analyzer (Applied Biosystems). Data analyses were performed with the GeneMapper 3.7 application software (Applied Biosystems).

Statistical analysis. Statistical significance ($P < 0.05$) was assessed by $\chi 2$ test for two degrees of freedom. Expected distribution of genotypes was calculated by Hardy-Weinberg equilibrium. The haplotypes were calculated using the Estimate Haplotype (EH) (Jurg Ott, Rockefeller University, New York) program based on the observed frequencies of the 1236C>T, 2677G>T/A and 3435C>T. Linkage disequilibrium (LD) between these three loci was found, resulting in the frequency differences between our results and haplotypes expected in case of lack of such an association (Table 6).

Results and Discussion

The *MDR1* is highly polymorphic gene spanning over 200 kb in human genome, however only a couple of the SNP located in the exonic sequence occur at high frequency. Thus, most of the studies are oriented towards elucidating the impact of these few polymorphisms on P-gp expression, function and also the drug-response of treated patients. In our study we have investigated the frequencies of seven *MDR1*-SNP-loci including the three most common SNP as well as related haplotypes in Slovak population. Figure 2 shows representative electrophoretograms from multiplex SNaPshot analyses of investigated SNP. In the three loci, -41A>G, -145C>G and -129T>C, all of the individuals were homozygous for wild-type allele and in the 4036A>G SNP, only few subjects were heterozygous. Therefore, we present only the data from highly heterozygous SNP in the Table 4. All of the observed genotype frequencies did not show significant deviation from the expected frequencies as calculated by Hardy-Weinberg equilibrium and all of the expected allelic frequencies are within the 95% confidence interval (CI). In the next, we focus on

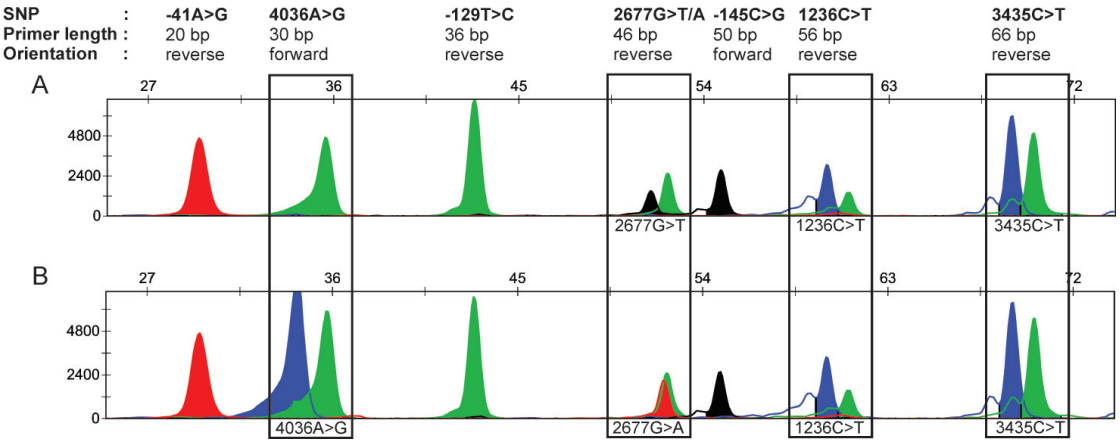

Figure 2. Analysis of SNaPshot products containing 7 SNP in *MDR1* gene. Capillary electrophoresis of SNaPshot products on ABI 310 Genetic Analyzer and SNP profiles of DNA samples analyzed with GeneMapper 3.7 as described in Materials and Methods. (A), An individual heterozygous for 2677G>A, 1236C>T and 3435C>T SNP. (B), An individual heterozygous for 4036A>G, 2677G>A, 1236C>T and 3435C>T SNP. Note: the C nucleotide appears as a black peak, and the G nucleotide is blue.

description of individual SNP that were highly polymorphic in Slovak population.

1236C>T: In a group of studied individuals, 35% (n=35) were homozygous for C allele, 20% (n=20) for T, and 45% (n=45) were CT heterozygotes. When comparing within other Caucasian populations, these allele frequencies are closest to those of German population [9]. For this silent polymorphism, the effect on the cyclosporine pharmacokinetic parameters was described previously pointing out a weak association between dose-adjusted C_{max} and dose adjusted AUC_{0-4} with the wild-type genotype, these parameters respectively being 16% and 14% lower in wild-type than in mutated allele carriers [15].

2677G>T/A: The most common genotype in the nucleotide position at 2677 of *MDR1* gene in our cohort was GT appearing in 43% (n=43), followed by GG in 32% (n=32) and TT in 21% (n=21) of individuals. We also identified four carriers of the rare A allele, two (2%) of them were TA and other two (2%) GA heterozygotes. This allele distribution is similar to that found in German or Russian population [9, 26]. Studies investigating the role of this SNP revealed its effect on the RNA level, further on the interaction between P-gp transporter and the substrate as well as on drug efflux [16, 17, 27]. Interestingly, it has been reported that this SNP is influencing the time to relapse and overall survival from relapse / refractory disease in AML patients [18, 19].

3435C>T: This was the very first silent SNP for which the effect on the P-gp protein level was clearly exhibited that led subsequently to the ever increasing interest on other SNP in the *MDR1* gene. The distribution of genotypes in our group was 33% (n=33), 45% (n=45) and 22% (n=22) for CC, CT and TT, respectively. Since this is the most studied SNP in the *MDR1* gene, the allele and genotype frequencies for various populations from around the world are known. The comparisons of these frequencies with our data are given in Table 5. The occurrence of this SNP differs within Caucasians with the range from 38% in Polish population [28] to 59% in Russian population [29]. It seems that the frequencies of genotypes at 3435 are rather consistent within individual races. As evident from Table 5, African population has a highest frequency of the C allele, up to 83% in Ghanaians. It is assumed that this high frequency is a consequence of natural selections resulting from selective advantage against gastrointestinal tract infections [30].

Haplotype analysis: As the superiority of haplotype analysis had been demonstrated in several studies [22–24], we also have estimated the haplotyope frequencies using the Estimate Haplotype (EH) program [31]. For the 2677-3435 haplotype, all six alternatives were present with the highest frequency for the 2677G-3435C (45.7%) followed by the 2677T-3435T (33.5%) and the rarest identified haplotype was the 2677A-3435T (0.02%). Obtained frequencies are comparable with those found in the most other Caucasian populations except the Germans where only four haplotypes were reported [22]. The haplotype frequencies are significantly different in African-American and Beninese population where the 2677G-3435C haplotype is present in 78.3% and 85.3% subjects, respectively. Only four haplotypes seem to exist in Beninese [32] and five in African-American population [33]. Recently published paper described the effect of the 2677G-3435T haplotype on AUC value after oral digoxin administration and also emphasized the notion that haplotype analysis was superior to considering only one SNP in the evaluation of the impact on P-gp phenotype [22]. We also evaluated haplotype frequencies for the 1236-2677-3435 loci. Ten from all twelve possible combinations were observed (Table 6) in Slovak population

Table 5. Allele and genotype frequencies of the *MDR1* 3435C>T observed in this study, compared with those found in other populations

Population	No. of subjects	Allele frequency		Genotype frequency			Reference
		C	T	CC	CT	TT	
CAUCASIANS							
Slovak	100	0.555	0.455	0.308	0.494	0.198	(this study)
German	461	0.45	0.54	0.208	0.505	0.286	[9]
Polish	122	0.62	0.38	0.42	0.41	0.17	[28]
Spanish	408	0.52	0.48	n.a.	n.a.	n.a.	[39]
Russian	290	0.46	0.54	0.21	0.49	0.30	[26]
Russian	59	0.41	0.59	0.20	0.41	0.39	[29]
UK	190	0.48	0.52	0.24	0.48	0.28	[39]
Portuguese	100	0.43	0.57	0.22	0.42	0.36	[39]
German	188	0.52	0.48	0.28	0.48	0.24	[8]
German	537	0.50	0.50	0.26	0.48	0.26	[30]
European American	37	0.46	0.54	n.a.	n.a.	n.a.	[11]
Northern Italian	106	0.54	0.46	0.26	0.55	0.19	[40]
Turkish	96	0.53	0.47	0.29	0.47	0.24	[4]
Polish	204	0.475	0.525	0.22	0.51	0.27	[41]
Czech	189	0.44	0.56	0.21	0.45	0.34	[42]
ASIANS							
Japanese	114	0.61	0.39	0.35	0.53	0.12	[43]
Chinese	132	0.53	0.47	0.32	0.42	0.26	[39]
Filipino	60	0.59	0.41	0.38	0.42	0.20	[39]
Japanese	50	0.57	0.43	0.34	0.46	0.20	[30]
Saudi	96	0.55	0.45	0.37	0.38	0.26	[39]
Southwest Asians	89	0.34	0.66	0.15	0.38	0.47	[39]
Chinese Kazakh	108	0.60	0.40	0.38	0.44	0.18	[44]
Chinese Han	165	0.62	0.38	0.38	0.48	0.14	[44]
Chinese Uygur	161	0.47	0.53	0.25	0.45	0.30	[44]
Malay	99	0.48	0.52	0.25	0.46	0.28	[23]
Indian	93	0.38	0.62	0.18	0.39	0.43	[23]
AFRICANS							
African American	88	0.84	0.16	0.68	0.31	0.01	[39]
Ghanaian	172	0.90	0.10	0.83	0.16	0.02	[30]
African American	41	0.78	0.22	0.61	0.32	0.05	[30]
Ghanaian	206	0.83	0.17	0.67	0.34	0.00	[39]
Kenyan	80	0.83	0.17	0.70	0.26	0.04	[39]
Sudanese	51	0.73	0.27	0.52	0.43	0.06	[39]
African American	23	0.74	0.26	n.a.	n.a.	n.a.	[11]

similarly to Asians [34] and Caucasians, but in contrast to eight present in African-American [35] and only six occurring in Beneneses [32]. The two major haplotypes observed were 1236C-2677G-3435C (42.2%) and 1236T-2677T-3435T (30.2%). The most frequent haplotype in Slovak population is also predominant in the Beninese (79.3%) and African-American (72.6%) populations [35]. It has been reported that the 1236C-2677G-3435C haplotype was associated with decreased overall survival and high probability of relapse in AML patients [36].

In conclusion, to our knowledge, the study we conducted represents the first attempt to estimate the frequencies of polymorphisms and haplotypes in the *MDR1* gene in Slovak population. The results reported here add to the data collected on SNP frequencies and haplotypes in this gene world-wide. They also show that in the future it is reasonable and feasible to perform the analysis of the *MDR1*-SNP in the Slovak pa-

Table 6. Linkage disequilibrium in *MDR1* gene: comparison of expected haplotype frequencies in case of no association and frequencies estimated on the basis of genotyping results

Nucleotide position			Frequency expected in case of no association	Frequency estimated on the base of genotyping results
1236	2677	3435		
C	G	C	0.182	0.422
C	T	C	0.136	0.052
C	A	C	0.006	0.017
C	G	T	0.143	0.051
C	T	T	0.107	0.034
C	A	T	0.005	0.003
T	G	C	0.132	0.038
T	T	C	0.099	0.031
T	A	C	0.005	0.000
T	G	T	0.103	0.049
T	T	T	0.078	0.302
T	A	T	0.004	0.000

tients before starting the treatment in order to evaluate the best drug-dosage in order to prevent the development of serious adverse drug reactions in some patients.

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