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Letter to the Editor

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First report on the distribution of 3435C>T *ABCB1/MDR1* polymorphism in healthy Bosniak population

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In 2000 Hoffmeyer et al. (1) reported reduced P-gp expression in humans to be correlated with the homozygous TT, which has more than 4-fold lower P-gp expression compared with homozygous CC. Available data suggest that decreased activity of P-gp due to 3435C>T mutation results in increased exposure of the intestinal epithelium to various toxic agents and might be associated with intestinal inflammatory disorders (2,3). Furthermore, recent studies have outlined that individuals with the 3435T allele may be susceptible to cancer (4).

The 3435C>T *ABCB1/MDR1* gene prevalence indicates a wide ethnic variation. Schaeffeler et al. (5) reported a higher frequency of the C allele in African populations, Ghanians and Afro-Americans, with 83% and 61% homozygosity respectively; in the same study only 26% of Caucasians and 34% of Japanese had this genotype. Researchers propose that the higher frequency of the C allele in African populations, compared with Caucasians and Asians, is caused by a selective advantage offered by this genotype against gastrointestinal tract infections in tropical areas (5). The highest frequency of the T allele was observed in Denmark (59%), medium frequency was found in Turkey and Italy (49% and 48%, respectively), and the lowest frequency was recorded in Croatia (45%) (6–9) (Table).

There is a lack of studies on this variant in the Bosniak population, and therefore the aim of this study was to estimate the allele frequency for the 3435C>T polymorphism in Bosniaks and to compare the results with data for other European populations. A comparison of the results is listed in the Table.

The subjects of the study consisted of 100 unrelated healthy individuals (82 female and 18 male) from Bosnia and Herzegovina. The mean age of the group was 58.8 (± 10.7) years. Amplification of *ABCB1/MDR1* (NCBI Reference Sequence NG_1045642) was performed by sequence-specific PCR in a thermocycler (SensoQuest), designed by a previously described technique by Drozdzik et al. (10). Amplification was followed by digestion of the 197 bp product using the *Sau3AI* restriction enzyme (Fermentas). *Sau3AI* digestion yielded fragments of 197 bp of homozygote CC; 197 bp, 158 bp, and 39 bp of heterozygote CT; and 158 bp and 39 bp of homozygote TT. The products were electrophoresed on a 3.5% agarose gel (Agarose DNA Grade, Electran), stained with DNA-star dye (Lonza, Inc.), and visualized under UV light. Statistical analysis was performed using SPSS (version 21) and the level of significance was set at $P < 0.05$. A χ^2 test was used to verify that genotype frequencies were fit with the Hardy–Weinberg equilibrium. Data sources were electronic databases, including Medline, Embase, and other major databases, which were searched from 1995 to July 2014.

In our study the genotype frequencies of CC, CT, and TT were 25%, 49%, and 26%, respectively, resulting in 3435T allele frequency of 50.5%. The results conformed to the expected Hardy–Weinberg equilibrium ($\chi^2 = 0.04$; $P = 0.841$).

Ethnicity is an important demographic factor associated with genetic differences. The rapid progress in the human genome analysis expands our knowledge about ethnic differences and responses to medications related to genotypic variants of key enzymes and proteins. Several preclinical and clinical studies have provided evidence for

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Table. Distribution of alleles and genotypes for the 3435C>T polymorphism of the *ABCB1/MDR1* gene in European populations.

Country	Ref.	Number of individuals	Allele frequencies (%)		Genotype frequencies (%)		
			C	T	CC	CT	TT
Bosnia and Herzegovina	Our study	100	49.5	50.5	25.0	49.0	26.0
Bulgaria	(10)	160	49.0	51.0	26.9	44.4	28.7
Croatia	(6)	120	55.0	45.0	26.9	57.1	16.0
Czech Republic	(11)	576	47.0	53.0	22.0	50.0	28.0
Denmark	(7)	765	41.0	59.0	16.5	48.2	35.3
France	(12)	222	54.0	46.0	28.0	52.0	20.0
Germany	(11)	1801	49.0	51.0	24.0	50.0	26.0
Hungary	(13)	503	47.0	53.0	22,0	50.0	28.0
Italy	(8)	450	52.0	48.0	26.0	53.0	21.0
Poland	(14)	202	50.0	50.0	25.4	50.2	24.4
Portugal	(15)	100	52.0	48.0	27.0	50.0	23.0
Russia	(16)	290	46.0	54.0	21.4	48.6	30.0
Scotland	(17)	370	48.0	52.0	22.0	51.0	27.0
Serbia	(18)	158	47.0	53.0	19.0	54.0	27.0
Slovenia	(19)	355	47.0	53.0	22.7	48.7	28.6
Spain	(20)	408	52.0	48.0	26.0	52.0	22.0
Turkey	(9)	174	51.0	49.0	28.2	46.0	25.8
UK	(21)	280	46.0	54.0	21.0	50.0	29.0

naturally occurring polymorphisms of the *ABCB1/MDR1* gene and their effects on drug absorption, distribution, and elimination, as well as risk of diseases (2–4).

The frequencies of the T allele in Western European countries were similar: 46% in France, 48% in Spain and Portugal, 51% in Germany, 52% in Scotland, and 54% in the UK (11–16). However, in Middle European countries the 3435T allele frequencies proved to be far more different: e.g., 45% in Croatians, 48% in Italians, and 59% in Danes (6–8). The frequency of the mutant allele T was lower in our study (50.5%) than it was reported in Denmark (59%) (7), but was almost exactly the same as the frequency reported in Poles (50%), Turks (49%), and Bulgarians (51%), and similar to the frequencies reported in Serbs, Slovenes, Czechs (53%), Hungarians, Russians, and British (54%) (9,17–22).

Our study was first for the Bosniak population and the obtained results might be relevant for further investigations of P-gp substrate drugs. They may also be relevant for studies on ethnic diversity and the prevalence of the 3435C>T *ABCB1/MDR1* polymorphism.

In conclusion, the distribution of the 3435C >T variant of the *ABCB1/MDR1* gene detected in a healthy Bosniak population did not differ significantly from those reported for other European populations, most probably due to the geographical location of Bosnia. Studies on larger cohorts with adequate female-to-male ratio are necessary to confirm this.

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