HUMAN GENETICS

Association of C3435T (rs1045642) Polymorphism of the *MDR1* Gene with the Increased Risk of Colorectal Cancer in Russian Females from Central Russia

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Abstract—The objective of this study was to examine associations of single nucleotide polymorphisms, rs1045642 within the *MDR1* gene and rs1799930 within the *NAT2* gene, with the risk of colorectal cancer (CRC) in the population of Central Russia. DNA specimens were obtained from 178 patients with CRC (87 males and 91 females) and 327 age-matched healthy controls (179 males and 148 females). Genotyping was performed using real-time PCR. Association of the studied SNPs with the risk of CRC was evaluated using logistic regression analysis. It was demonstrated that *MDR1* rs1045642 polymorphism was associated with the increased risk of CRC after correction for gender, age, and smoking ($OR = 1.41$, 95% $CI = 1.09–1.83$; $P = 0.008$). A gender-stratified analysis showed that *MDR1* rs1045642 was associated with the increased risk of CRC only in females ($OR = 1.62$, 95% $CI = 1.11–2.35$; $P = 0.01$). In males, no association between *MDR1* rs1045642 and CRC was found. Association between *MDR1* rs1045642 and the increased risk of colorectal cancer in Russian females from Central Russia was revealed.

INTRODUCTION

Colorectal cancer (**CRC**), including colon and rectal cancer, is one of the most common cancers worldwide [1]. Previous epidemiological studies have shown that genetic susceptibility factors together with environmental factors (such as smoking, nutrition, bacterial toxins, etc.) can increase the risk of CRC [2]. However, the exact mechanisms underlying the development of this malignant tumor of the digestive system remain unclear.

Arylamine N-acetyltransferase 2 (NAT2) is an enzyme involved in the Phase II of xenobiotic biotransformation. It catalyzes the metabolism of environmental carcinogens (aromatic hydrocarbons, heterocyclic amines, and hydrazines), as well as some polar compounds (such as methyl and acetyl) [3]. NAT2 is most highly expressed in the liver and intestinal mucosa. The gene encoding NAT2 is polymorphic. The G > A substitution at the position 590 of *NAT2* (rs1799930) determines the acetylator phenotype, which is subdivided into rapid and slow ones. The acetylator status, in turn, can affect the metabolism of certain carcinogens, the activation/inactivation of which may be at risk of CRC. Analyses of associations between the *NAT2* acetylator phenotypes and CRC showed conflicting results. For instance, Probst-Hensch et al. [4] found an inverse correlation between the *NAT2* rapid acetylator genotype and colorectal adenoma in black Americans; however, in white Americans, this genotype was associated with the increased risk of this disease. Other studies have also shown that the rapid *NAT2* genotype played an important role in susceptibility to colorectal cancer [5]. At the same time, previous meta-analysis showed a lack of association between *NAT2* rs1799930 and CRC [6].

The multidrug resistance 1 gene (***MDR1***, also called the ATP-binding cassette transporter, subfamily

B, member 1 (*ABCB1*)) encodes transmembrane glycoprotein, P-glycoprotein (P-gp), participating in the Phase III of xenobiotic biotransformation [7]. C3435T (rs1045642), one of the most studied SNPs in the *MDR1* gene, affects the P-gp functional properties [8]. In 2005, Kurzawski et al. [9] were analyzed, for the first time, an association between *MDR1* C3435T and the development of CRC in the Polish population. It was demonstrated that *MDR1* 3435TT genotype was associated with a 2.7-fold higher risk of colon cancer. Then, the number of studies on the association of this polymorphism with the development of CRC increased considerably with most of them performed on Asian populations. However, the results were contradictory [10−12]. For instance, Komoto C. et al. [11] revealed the effect of *MDR1* rs1045642 on the development of CRC in the Japanese population [11]. At the same time, in two other studies performed in Korea, no associations between rs1045642 *MDR1* and CRC were found [10, 12]. These contradictions can be explained by the small sample sizes of the studied cohorts and low statistical power of the studies. A recent meta-analysis showed a lack of association between *MDR1* C3435T and the risk of colorectal cancer in Europeans [13]. Another recent meta-analysis showed the association between *MDR1* C3435T polymorphism and a decreased risk of CRC in Asians [14].

Associations between *NAT2* rs1799930 and *MDR1* rs1045642 polymorphisms and the risk of colorectal cancer in the population of Central Russia were not studed yet.

The objective of this study was to analyze the associations between *NAT2* rs1799930 and *MDR1* rs1045642 polymorphisms and the risk of colorectal cancer in the population from Central Russia.

MATERIALS AND METHODS

A total of 505 unrelated Russian individuals from Kursk region was examined; written informed consent was obtained from all participants prior to entering the study. The study included 178 CRC patients (87 males and 91 females) who underwent inpatient treatment at the Kursk Regional Clinical Oncology Center between 2013 and 2017 [15]. The control group consisted of 327 healthy volunteers (179 males and 148 females) without a history of chronic diseases. Patients were included in the study group only after verification of final diagnosis of the disease, confirmed by clinical, laboratory and instrumental methods. The study was approved by the Regional Ethics Committee of Kursk State Medical University.

The mean age of CRC patients was 66.92 ± 9.27 years; the mean age of the control group individuals was slightly higher − 68.71 ± 8.44 years ($P = 0.02$). The groups (CRC patients and controls) were frequency-matched according to gender ($P > 0.05$). Venous blood samples were obtained from all individ-

uals. Genomic DNA was isolated from peripheral blood by the standard phenol-chloroform extraction method. Genotyping of *NAT2* rs1799930 and *MDR1* rs1045642 polymorphisms was performed by real-time PCR using allelic discrimination assay with TaqMan probes on a CFX96 amplifier (Bio-Rad, USA). Regenotyping of 10% of the studied samples taken randomly and in the absence of information on the status of the disease showed 100% reproducibility of the original results.

Associations of alleles with the risk of CRC were performed using logistic regression analysis. To assess association of genotypes with the disease, the odds ratio (*OR*) and 95% confidence interval (*CI*) values calculated for the log-additive regression model were used. All calculations were performed adjusted for gender, age, and smoking in the SNPStats software program, available online (https://www.snpstats.net/start.htm). A value of $P \le 0.05$ was taken as statistically significant.

RESULTS AND DISCUSSION

The genotype frequency distributions of the studied SNPs in the patient and control groups were in Hardy–Weinberg equilibrium ($P > 0.05$). We were unable to genotype *MDR1* rs1045642 polymorphism in one DNA specimen from the CRC patient group, as well as in one DNA specimen from the control group. The results of the analysis of associations of the studied polymorphisms with SRS risk are presented in Table 1. According to the results, *NAT2* rs1799930 was not associated with the risk of colorectal cancer; at the same time, *MDR1* rs1045642 was associated with the risk of CRC even after adjustment for gender, age, and smoking habit (Table 1).

Taking into consideration the sexual dimorphism of associations of the genetic markers with multifactorial diseases, at the next step we performed gender-stratified analysis of rs1045642 in the MDR1 gene with the risk of colorectal cancer. In males, no associations between *MDR1* rs1045642 and the risk of CRC were detected. At the same time, in females, *MDR1* rs1045642 polymorphism was associated with the risk of CRC, taking into account adjustment for gender, age, and smoking habit (Table 2).

A number of studies accumulated over the last years provide evidence on the important role of genetic factors in the pathogenesis of CRC [9−11].

The *MDR1* gene, which encodes the ATP-binding cassette transporter, P-gp, is mapped to chromosomal region 7q21.12. It contains 29 exons and encodes a protein containing 1280 amino acids [7]. To date, more than 50 single nucleotide polymorphisms have been identified in the *MDR1* gene. A recent study showed that synonymous substitution (C3435T) was one of the most functionally important polymorphisms in the *MDR1* gene, which changed the conformation of the encoded P-gp and affected the timing of

Table 1. Analysis of associations of *NAT2* rs1799930 and *MDR1* rs1045642 with the risk of colorectal cancer

	Analysis of associations of *NAT2* rs1799930 with the risk of CRC, combined groups				
	Minor allele/genotypes	Patients (*N* = 178)	Control (*N* = 327)	P^1	*OR* (95% CI)[2]
Minor allele frequency	*A*	0.272	0.291	0.59	0.92 (0.69−1.22)
Genotype frequencies, *N* (%)	*GG*	93 (52.2%)	167 (51.1%)		0.93 (0.70−1.24)
	GA	73 (41%)	130 (39.8%)	0.63	
	AA	12 (6.7%)	30 (9.2%)		
	Analysis of associations of *MDR1* rs1045642 with the risk of CRC, combined groups				
	Minor allele/genotypes	Patients (*N* = 177)	Control (*N* = 326)	P^1	*OR* (95% CI)[2]
Minor allele frequency	*T*	0.531	0.440	**0.01***	**1.44 (1.11−1.87)**
Genotype frequencies, *N* (%)	*CC*	41 (23.2%)	106 (32.5%)		**1.41[!] (1.09−1.83)[!]**
	CT	84 (47.5%)	153 (46.9%)	**0.008*[!]**	
	TT	52 (29.4%)	67 (20.6%)		

[1] *P* value with adjustment for gender, age, and smoking habit. [2] Odds ratio and 95% confidence interval. [3] Akaike information criterion. * Statistically significant differences between groups are demonstrated. [!] Indices calculated for the log-additive regression model with adjustment for gender, age, and smoking habit.

Table 2. The influence of gender on associations of *MDR1* rs1045642 with the risk of colorectal cancer

	Analysis of associations of *MDR1* rs1045642 with the risk of CRC, males				
	Minor allele/genotypes	Patients (*N* = 86)	Control (*N* = 180)	P^1	*OR* (95% CI)[2]
Minor allele frequency	*T*	0.500	0.444	0.27	1.25 (0.87−1.80)
Genotype frequencies, *N* (%)	*CC*	20 (23.3%)	58 (32.2%)		1.25 (0.87−1.79)
	CT	46 (53.5%)	84 (46.7%)	0.23	
	TT	20 (23.3%)	38 (21.1%)		
	Analysis of associations of *MDR1* rs1045642 with the risk of CRC, females				
	Minor allele/genotypes	Patients (*N* = 91)	Control (*N* = 146)	P^1	*OR* (95% CI)[2]
Minor allele frequency	*T*	0.560	0.435	**0.01***	**1.65 (1.14−2.40)**
Genotype frequencies, *N* (%)	*CC*	21 (23.1%)	48 (32.9%)		**1.62[!] (1.11−2.35)[!]**
	CT	38 (41.8%)	69 (47.3%)	**0.01*[!]**	
	TT	32 (35.2%)	29 (19.9%)		

[1] *P* value with adjustment for gender, age, and smoking habit. [2] Odds ratio and 95% confidence interval. [3] Akaike information criterion. * Statistically significant differences between groups are demonstrated. [!] Indices calculated for the log-additive regression model with adjustment for gender, age, and smoking habit.

cotranslational folding and introduction of P-gp into the membrane, thereby changing the structure of substrate and inhibitor interaction sites [8]. In addition, Hoffmeyer et al. [16] showed a considerable decrease in the level of MDR1 protein in duodenal tissues of homozygous 3435TT carriers. Thus, rs1045642 polymorphism affects both the *MDR1* gene expression and P-glycoprotein activity.

Data on association of *MDR1* C3435T with the risk of CRC are contradictory. In some studies, a pronounced association between *MDR1* C3435T and susceptibility to CRC was demonstrated [17, 18]. In other studies, association was not confirmed [10−12, 19]. To study the association of the *MDR1* gene with the risk of CRC, a number of meta-analyses were performed. For example, according to the results of a meta-analysis which included ten studies of European populations, no association between *MDR1* C3435T polymorphism and colorectal cancer was detected [13]. However, He T. et al. [20] showed that combined haplotypes of several *MDR1* SNPs, including rs1045642, could be a reliable marker to determine the susceptibility to CRC in Europeans, while *MDR1* rs1045642 polymorphism was highly associated with the risk of CRC in Asians. Another large meta-analysis based on 39 studies of different forms of cancer showed that carriage of the *MDR1* 3435TT genotype was associated with an increased risk of different forms of cancer in European populations [21].

It is known that the relative contribution of genetic markers to susceptibility to CRC may vary depending on the ethnic group. Moreover, a recent study showed a considerable difference in the prevalence of the *MDR1* 3435TT genotype among healthy Asians (27.8%) and Europeans (49.4%) [22]. Thus, the relative contribution of *MDR1* C3435T polymorphism to the development of CRC may vary in different populations, and the role of *MDR1* rs1045642 in colon carcinogenesis remains unclear.

The present study involved 178 CRC patients and 327 individuals from the control group. This is the first study of association between *MDR1* C3435T polymorphism and susceptibility to CRC in the Russian population. The data obtained showed that *MDR1* rs1045642 was associated with the increased risk of CRC in the population of Central Russia.

The ATP-binding cassette transporter B1 (ABCB1, P-glycoprotein, multidrug resistance protein 1 (MDR1)) functions as unidirectional transporter that mediates the outflux of a wide range of endogenous and xenobiotic compounds, thereby protecting cells against potentially toxic substances. ABCB1 has unusually wide multispecificity for numerous substrates, most of which are hydrophobic [23]. The localization of P-gp in the apical membrane of enterocytes points to its role in the efflux of possibly toxic xenobiotics out of the intestine [24]. It is noteworthy that the highest aggregation of P-gp was observed in distal part of digestive tract, especially in the colorectal region [25]. In addition, association between the *ABCB1* gene and the Wnt/β-catenin signaling cascade was revealed; the last one is the most common dysfunction in rare hereditary forms of CRC [26]. Moreover, in vitro studies demonstrated that *ABCB1* expression was observed in cells with *P53* mutations (*P53* mutations are found in 50% of CRC cases) [27].

Considering that the main function of the ABCB1 product is the efflux of a number of toxic xenobiotic compounds out of cells, it can be suggested that altered P-gp function can lead to the development of intracellular toxic and chemical stress and, thereby, increase the risk of DNA damage by the products of incomplete xenobiotic metabolism (potential carcinogens), mediating the susceptibility of colon cells to tumor transformation.

In addition, it should be noted that the present study showed sex-specific effects in association of *ABCB1* C3435T polymorphism with the risk of CRC. In most countries of the world, the morbidity and mortality rates from CRC are considerably higher among males than among females [28]. On the other hand, several studies reported higher survival rates in females with CRC compared to males [29, 30]. First, gender can reflect different levels of environmental factors associated with occupational exposure, diet, or lifestyle. Second, sex hormones can also affect the expression of genes associated with the development of this disease. It should be noted that steroid hormones, such as progesterone, are able to modulate P-gp expression in some tissues, as evidenced by studies in mice [31]. On the other hand, SNPs can alter *ABCB1* expression, affecting the regulatory sequences that are targeted by steroid hormones, or can alter the ability of ABCB1 to metabolize specific substances, the consumption of which may be sex-dependent. This hypothesis is consistent with the results of Nakamura et al. [32], who suggested that serum cortisol and aldosterone levels in females could depend on *ABCB1* rs1045642 polymorphism [32].

Thus, the results of the present study demonstrated that *MDR1* C3435T polymorphism was associated with an increased risk of CRC in the population from Central Russia, exclusively in females. Further studies on a larger sample size, as well as replication studies, are required to confirm the role of *MDR1* C3435T (rs1045642) in the pathogenesis of colorectal cancer, especially in terms of gene-gene and gene−environment interactions.

FUNDING

COMPLIANCE WITH ETHICAL STANDARDS

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants involved in the study.

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Translated by N. Maleeva

SPELL: 1. explaned, 2. studed