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Associations of Polymorphisms of the *CYP*1*A*1 and *CYP*1*B*1 Cytochrome P450 Genes with Breast Cancer in Kazakhstan

T. S. Balmukhanov*, A. K. Khanseitova, V. G. Nigmatova, S. P. Varchenko, Sh. Zh. Talaeva, N. A. Aitkhozhina
Structural and Functional Genomics Laboratory, Institute of Molecular Biology and Biochemistry, Almaty, Kazakhstan
Email: *imbbtimur@mail.ru

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ABSTRACT

Associations of polymorphisms in rs4646903 site of *CYP*1*A*1 and rs1056836 site of *CYP*1*B*1 genes with the breast cancer (BC) were studied in two main ethnic groups of Kazakhstan Republic (Kazakhs and Russians). Total number of BC patients was 181, controls—397. The statistically significant differences were revealed in allele frequencies ($\chi^2 = 5.93$, $p = 0.004$) and in genotypes distribution ($\chi^2 = 8.71$, $p = 0.015$) in rs4646903 site of *CYP*1*A*1 gene in Kazakh but not in Russian group. The study of *CYP*1*B*1 rs1056836 site demonstrated differences in genotype distributions ($\chi^2 = 7.48$, $p = 0.023$) between BC patients and controls in Russian but not in Kazakh ethnic group.

Keywords: Breast Cancer; Gene Polymorphism; *CYP*1*A*1; *CYP*1*B*1; Kazakhstan

1. Introduction

Cancers in hormone-respective tissues, including breast cancers occur at high incidence rates worldwide. Numerous studies investigating the relationship between breast cancer (BC) and polymorphisms in candidate genes involved in xenobiotic detoxification have been reported earlier including meta- and pooled analysis of cytochrome P450 1B1 polymorphism association with breast cancer published and unpublished data from Environmental Carcinogenes Database [1]. Racial differences in breast cancer risks of hormone receptors subtypes of BC also have been previously reported [2]. Comparative analysis of SNP in estrogen-metabolizing enzymes for ovarian, endometrial and breast cancer in Novosibirsk was performed in Russia [3]. Interethnic differences between Russians, Tatars and Bashkirs in the frequency of the *CYP*1*A*1 and *CYP*1*A*2 are described in Bashkortostan, Russia [4].

Republic of Kazakhstan is a multinational state situated in the middle of Central Asia with the population about 17 million, mainly Kazakhs—Asians and Russian—Caucasians.

No studies describing associations of BC with Cytochrome P450 family genes have been earlier performed in Kazakhstan.

*Corresponding author.

2. Materials and Methods

A total of 181 breast cancer patients and 397 of healthy age-matched controls (blood-donors with no family history of cancer) were analyzed for the polymorphisms of *CYP*1*A*1 at rs4646903 and *CYP*1*B*1 at rs1056836 by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and two-stage PCR reaction, respectively. Peripheral blood samples were collected from the subjects with informed consent to participation in this study. The average age of the BC patients was 50.3 ± 11.6 years (Kazakhs), 55.7 ± 11.7 (Russians) and of controls 50.07 ± 8.47 (Kazakhs), 54.8 ± 5.9 (Russians).

Genomic DNA was isolated from blood samples using Axygen kits (USA) according to the manufacturer's instructions. The PCR reaction was carried out in a total volume of 20 µl, 1 x buffer containing 67 mM Tris HCl, pH 8.8, 16.6 mM $(NH_4)_2SO_4$, 2 mM $MgCl_2$, 0.01% Tween 20, 0.15 mg/ml BSA, 2 pM of each primers, 0.25 mM each of four dNTPs, and 1 unit of Taq DNA polymerase (SibEnzime, Novosibirsk, Russia).

The polymorphism at rs4646903 of *CYP*1*A*1 gene was analyzed using the following primers: forward 5'-CAGTGAAGAGGTGTAGCCGC-3' and reverse 5'-TAGGAGTCTTGTC-TCATGCC-3'. The thermocycling conditions were as follows: initial denaturation at 94˚C - 5

min, amplification at 94˚C - 1 min, 61˚C - 1 min, 72˚C - 1 min - 30 cycles, final elongation - 72˚C, 7 min [5]. Amplified DNA fragment of 340 bp, containing the region of interest, was subjected to restriction enzyme digestion with MspI. The enzyme cleaves a C/CGC sequence at *CYP*1*A*1 3' region, generating 200 bp and 140 bp fragments.

Polymorphism at rs1056836 site of *CYP*1*B*1 gene was analyzed by means of two-stage PCR reaction [6]. At the first stage the following primers were used: F 5'-ATGCGCTTCTCCAGCTTTGT-3'; R 5'-TATGGAGCACACCTCACCTG-3'. The DNA fragment of 623 bp amplified in the first stage serves as a template for the second stage of PCR. The forward primer at the second stage was the same as in the first stage, however, the reverse primers used were specific at 3'end: R 5'-TCCGGGTTAGGCCACTTCAC-3'; R 5'-CGGGTTAGGCCACTTCAG-3'. The thermocycling conditions of both PCR reactions were as following: initial denaturation at 94˚C - 5 min, amplification at 94˚C - 1 min; 55˚C - 1 min; 72˚C - 1 min - 30 cycles; final elongation - 72˚C, 8 min.

The differences were estimated using Pearson's χ^2 test ($p < 0.05$) by checking the correspondence of genotypes distribution to the Hardy-Weinberg equilibrium. The OR (odds ratio) and 95% CI (confidence interval) were used to evaluate the association between genotypes and breast cancer susceptibility.

Fisher's exact test was used when the values of genotypes were nonrandomly distributed in table cells (one of the meanings less than 6). Statistical calculations were performed using Microsoft Excel and Statistica 2007 software.

3. Results and Discussion

The CYP1A1 gene is located at 15 chromosome (15q22 - q24.1), contains 7 exons and spans about 6000 base pairs. We are testing the association of BC with the single-nucleotide polymorphism T/C at rs4646903 (ancestral allele is T) located in 3'-nontranslated sequence in 242 position at the end of 7th exon. Although the functional role of this polymorphism is not yet fully determined, its associations with different types of cancers were reported [7-9]. Results of investigations performed in different populations showed controversial results. For example, it was shown that the genotype of clinical significance for Chinese women is CC [10], whereas for Korean women T allele was shown to be a risk associated [11] and for the women of North America [12] the correlations of polymorphism in this site with BC were not evaluated.

At the first stage of our investigation we have determined the genotypes distribution and allele frequency among Kazakh and Russian ethic groups and compared the data with that of other ethnic groups obtained from National Center for Biotechnology Information (NCBI) database. As it can be seen from **Table 1** allele frequency in Kazakhs (Asian type) and combined Asian group (CHB + JPT) are similar. In Russian group (Caucasian type) genotypes distribution and allele frequency are more close to those indices in Caucasian groups. Also, the significant differences in genotype distribution with P = 1.74 * 10 - 6 and in allele frequency with P = 5.70 * 10 - 7 were registered between Kazakh and Russian control groups.

The results of genotypes distribution and allele frequency analysis at rs4646903 site of gene *CYP*1*A*1 among BC patients of the Kazakh and Russian ethnic groups and controls are summarized in **Table 2**.

As it can be seen from the results, in the Russian group no significant differences were found in the genotypes distribution and allele frequency between cancer cases and controls. In contrast, the statistically significant differences in genotypes distribution and allele frequency between BC patients and controls were found at rs4646903 polymorphism in the Kazakh group. The odds

Table 1. Genotypes distribution and allele frequency at rs4646903 site of *CYP1A1* gene in several ethnic groups according NCBI database and to the author's data.

Group	Genotypes distribution and allele frequency				
	C/C	C/T	T/T	C	T
NCBI-CAUC	0	0.379	0.621	0.190	0.810
NCBI-AFR1	0.130	0.304	0.566	0.283	0.717
NCBI-HISP1	0.087	0.391	0.522	0.283	0.717
NCBI-CHB + JPT	nd	nd	nd	0.375	0.625
Kazakhs	0.078	0.471	0.451	0.313	0.687
Russians	0.033	0.233	0.733	0.150	0.850

a. CAUC1—Caucasian; AFR1—African/African American; HISP1—Hispanic; CHB + JPT—Han Chinese in Beijing + Japanese in Tokyo, nd—no data.

Table 2. Genotypes distribution and allele frequency at rs4646903 site of gene *CYP1A1* in the Kazakh and Russian ethnic groups.

Nationality	Alleles/ genotypes	Frequency		OR	CI (95%)	χ^2	P
		Patients, N = 119	Controls, N = 206				
KZ	T	0.592	0.687	0.66	0.48 - 0.92	5.93	0.01 (0.004)
	C	0.408	0.313	1.51	1.08 - 2.10		
	TT	0.370	0.451	0.71	0.45 - 1.13	8.71	0.01 (0.015)
	TC	0.445	0.471	0.90	0.57 - 1.42		
	CC	0.185	0.078	2.69	1.35 - 5.36		
	Alleles/ genotypes	Patients N = 59	Controls, N = 150	OR	CI (95%)	χ^2	P
RU	T	0.890	0.850	1.43	0.74 - 2.75	1.12	0.29 (0.074)
	C	0.110	0.150	0.70	0.36 - 1.35		
	TT	0.780	0.733	1.29	0.63 - 2.63	2.12	0.35 (0.481)
	TC	0.220	0.233	0.93	0.45 - 1.91		
	CC	0.000	0.033	0.22	0.01 - 4.08		

Comments. KZ—Kazakhs, RU—Russians. In the brackets the means after correction the data according Fisher's test are shown.

ratio (OR) for homozygotes CC in this group was equal to 2.69 (CI 95%: 1.35 - 5.36) and this value can be regarded as an indication to the association of C/T polymorphism (allele C) with breast cancer in Kazakh ethnic group.

The results presented for the Kazakh group are in agreement with studies describing the presence of an association with BC in the population of China [10] and of Mexico: OR = 1.95, CI = 1.13 - 3.36 [13].

In Russian group no differences were found either in genotypes distribution or in the allele frequency of polymorphism at rs4646903 site. Interestingly, the absence of association of this polymorphism with BC in Russian ethnic group shown in the current study does not coincide with the results of two similar investigations performed in Russians inhabiting Novosibirsk, Russia, where significant differences in allele and genotype frequencies at rs4646903 site of gene *CYP*1*A*1 between patients and controls were described.

We had compared the allele and genotype T-C-TT-TC-CC frequency for the investigated groups of Russians in Kazakhstan and Russia: 0.850 - 0.150 - 0.733 - 0.233 - 0.033—presented results; 0.896 - 0.104 - 0.796 - 0.201 - 0.003—Novosibirsk [14]; 0.888 - 0.112 - 0.775 - 0.225 - 0.000—Novosibirsk, [3].

These data show the presence of significant differences in genotype distribution between ethnic Russians, inhabiting Novosibirsk, Russia and Kazakhstan (χ^2 = 3.874, P = 0.049).

Earlier we have received the similar data describing the specificities of genotypes of ethnical Russians inhabiting Kazakhstan [15].

The *CYP*1*B*1 gene is located at 2 chromosome (2p22 - p21), contains 3 exons and 2 introns, and spans about 7 800 base pairs.

We have analyzed the association of BC with the single-nucleotide polymorphism C/G (rs1056836), located at 1666 position in 3rd exon, leading to leucine/valine aminoacid substitution at 432 codon (Leu/Val). This substitution (Val432 allele, G) results in three fold increase of 4-hydroxylase activity compared with Leu432 allele (C). The similar increase of catalytical activity was also shown for the other polymorphic variants: Gly48, Ser119, Ser453 [6].

In **Table 3**, the values of genotypes distribution and allele frequency in rs1056836 site of gene *CYP1B1* in the main world ethnic groups according HapMap, NCBI and author's data are presented.

Genotypes distribution and allele frequency at rs1056836 site of gene *CYP*1*B*1 in the Russian ethnic group are similar to those indices in the group Utah residents with Northern and Western European ancestry (CEU).

In the Kazakh group the values of genotypes distribution and allele frequency at rs1056836 site were intermediate between those of CEU and the combined Asian group of Han Chinese in Beijing, and Japanese in Tokyo (CHB & JPT).

The analysis of this polymorphism performed in China showed the elevated risk of BC in carriers of CC genotype with OR = 2.3, 95% CI = 1.2 - 4.5 in Ningxia Hui region [16] and OR = 2.8, 95% CI = 1.04 - 7.51 in Shanghai [17]. The positive associations of this polymorphism with BC were also found in Turkey [18] and Nigeria [19].

The genotypes distribution and allele frequency at rs1056836 site of *CYP*1*B*1 gene in the Kazakh and Russian ethnic groups of BC patients and controls are summarized in **Table 4**.

In the Russian group the statistically significant difference (χ^2 = 7.48, P = 0.02) in genotype distribution was differenct in genotypes distribution and allele frequency type. This result differs from the results of other Cauca sian populations [2,20].

Positive association of polymorphism at rs1056836 of

Table 3. Genotypes distribution and allele frequency in rs1056836 site of gene *CYP*1*B*1 in some world ethnic groups according to NCBI and author's data.

Group	Genotypes distribution and allele frequency				
	C/C	C/G	G/G	C	G
HapMap-CEU	0.336	0.434	0.230	0.553	0.447
HapMap-CHB	0.774	0.256	0	0.872	0.128
HapMap-JPT	0.821	0.167	0.012	0.905	0.095
Kazakhs	0.541	0.404	0.055	0.743	0.257
Russians	0.374	0.419	0.207	0.584	0.416

CEU—Utah residents with Northern and Western European ancestry, CHB—Han Chinese in Beijing, JPT—Japanese in Tokyo.

Table 4. Genotypes distribution and allele frequency at 432 codon of *CYP*1*B*1 (rs1056836) in the Kazakh and Russian ethnic groups.

Nationality	Alleles/ genotypes	Frequency		OR	CI (95%)	χ^2	P
		Patients, N = 121	Controls, N = 218				
KZ	C	0.789	0.743	1.29	0.89 - 1.89	1.81	0.18 (0.031)
	G	0.211	0.257	0.77	0.53 - 1.13		
	CC	0.620	0.541	1.38	0.88 - 2.17		
	CG	0.339	0.404	0.76	0.48 - 1.20	1.99	0.37 (0.392)
	GG	0.041	0.055	0.74	0.25 - 2.15		
	Alleles/ genotypes	Patients, N = 60	Controls, N = 179	OR	CI (95%)	χ^2	P
RU	C	0.617	0.584	1.15	0.75 - 1.75	0.40	0.53 (0.703)
	G	0.383	0.416	0.87	0.57 - 1.33		
	CC	0.317	0.374	0.77	0.42 - 1.44		
	CG	0.600	0.419	2.08	1.15 - 3.77	7.48	0.02 (0.023)
	GG	0.083	0.207	0.35	0.13 - 0.93		

Comments. KZ—Kazakhs, RU—Russians.In brackets the means after correction the data according Fisher's test are shown.

*CYP*1*B*1 gene with BC was found in the population of Slovenia but only in combination with polymorphism in COMT gene (OR, 2.0; 95% CI, 1.1 - 3.5) [21], and of USA (OR = 1.2; 95% CI 0.9 - 1.6) [22] for individuals homozygous by minor allele.

In the Kazakh ethnic group no associations of genotypes distribution and allele frequency at rs1056836 site of *CYP*1*B*1 gene with BC were found. These findings are in agreement with the results of similar studies performed in Asian cohorts [23,24] and with meta- and pooled analysis of associations of cytochrome P450 1B1 genes polymorphism and breast cancer [1].

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