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HUMAN GENETICS

The Role of Polymorphic Variants of Gene Components of the PTEN/PI3K/AKT Signaling Pathway in the Development of Prostate Cancer

I. R. Gilyazova[a, *], E. A. Ivanova[a, **], M. A. Bermisheva[a], M. V. Loginova[b], D. D. Asadullina[a], R. R. Ishemgulov[b], A. T. Mustafin[b], V. N. Pavlov[b], and E. K. Khusnutdinova[a, b]

[a] *Institute of Biochemistry and Genetics—Subdivision of the Ufa Federal Research Center, Russian Academy of Sciences, Ufa, 450054 Russia*

[b] *Bashkir State Medical University, Ufa, 450008 Russia*

**e-mail: gilyasova_irina@mail.ru*

***e-mail: lissa987@yandex.ru*

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Abstract—The aim of this study was to search for associations of genotypes and alleles of polymorphic loci of the PTEN/PI3K/AKT pathway genes rs2494750 of *AKT1*, rs2735343, rs2299941, rs10490920 of *PTEN*, rs17878362 of *TP53*, and rs2699887 of *PIK3CA* with the risk of prostate cancer development. As a result of comparison allele and genotype frequencies between the general sample of prostate cancer patients and the control group of healthy individuals, it was found that the *CG* genotype of the polymorphic locus rs2735343 of *PTEN* is associated with an increased risk of developing the disease (OR = 1.38, 95%CI = 1.02–1.87, p = 0.04), whereas the *GG* genotype showed a decrease in the frequency of occurrence in the group of patients compared with the control (OR = 0.74, 95%CI = 0.55–0.99, p = 0.05). When stratifying the group of patients with prostate cancer, depending on histopathological characteristics, it was revealed that the rs2735343**C* allele is associated with an increased risk of bilateral lesions of both prostate lobes and invasion of seminal vesicles. With allowance for further validating studies, the results of this work can be used to create a panel of molecular markers for disease prognosis and assessment of tumor characteristics.

Keywords: prostate cancer, polymorphic variants of genes, PTEN/PI3K/AKT pathway

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INTRODUCTION

Prostate cancer (PC) is a malignant neoplasm arising from the epithelium of the alveolar-cell elements of the prostate gland. In terms of the incidence of malignant tumors among the male population, prostate cancer ranks second. Approximately one million new cases of the disease are diagnosed worldwide each year [1]. The main cause of death in prostate cancer is metastasis and the formation of a castrate-resistant form of the disease, which is not treatable using currently existing therapeutic tactics. Prostate cancer has a wide range of clinical manifestations, from localized and indolent disease to aggressive forms, accompanied by metastasis. The most commonly used markers for the diagnosis and monitoring of prostate cancer are prostate-specific antigen (PSA), pathological Gleason scale, pathological stage, and tumor volume [2]. However, these markers do not always allow timely diagnosis and prediction of the course of the disease. In this regard, genomic markers have extremely high prospects, making it possible to assess the prognosis, stratify tumors by risk, monitor the clinical response to therapy, and much more [3].

One of the most commonly dysregulated cell signaling pathways in prostate cancer is the phosphoinositide 3-kinase/serine threonine kinase (PI3K/AKT) pathway. It is known that PI3K is able to activate the AKT/mTOR pathway, the main function of which is to inhibit apoptosis and increase cell survival, which, in turn, can lead to stimulation of tumor growth. It is also known that the PI3K/AKT pathway performs a central function in the epithelial-mesenchymal transition, a key process in tumor progression and metastasis [4]. PI3K/AKT is regulated by the phosphatase and tensin homolog PTEN, exhibiting the properties of a classical tumor suppressor [2]. In turn, PTEN transcription is activated by p53, a known cell cycle regulator. Conversely, a stimulus-induced increase in PTEN transcription and protein translation leads to the induction of p53 [5].

Single nucleotide polymorphic variants (SNPs) are important DNA variations that create diversity among individuals and contribute to different phenotypes,

traits, and diseases [6]. Numerous studies have shown that there is an association between polymorphic variants of the genes included in the PI3K/PTEN/AKT pathway and the development of malignant tumors, including prostate cancer [7–9]. To date, among the genes of the PI3K/PTEN/AKT pathway, there are about a thousand SNPs located in the coding region. It was noted that, among these SNPs, there are functional polymorphic variants that can affect carcinogenesis by modulating the transcriptional activity of genes or changing microRNA binding sites [10]. For example, if there is an allele *T* in polymorphic variant rs2295080 of the gene *mTOR*, there are increased levels of mTOR mRNA compared to the allele *G* in patients with renal cell carcinoma and colorectal cancer. Another polymorphic variant, rs2536, located in the 3'UTR region of mTOR, is able to influence binding to miRNAs in the presence of an alternative allele [11]. In the gene *PTEN*, a polymorphic variant rs701848 was previously found, located in close proximity to the 3'-region, where the microRNA binding sites are concentrated. Numerous studies have shown that rs701848 is associated with the risk of developing various types of malignant tumors, including kidney and prostate cancer [12, 13]. In the gene *AKT1*, one of the well-studied polymorphic variants is rs2494752, located in the 5'-UTR region. It is assumed that this polymorphic variant can modulate transcription and translation of AKT1, since it is located in the binding region of the transcription factor [10]. Another polymorphic variant rs2494750 of the gene *AKT1* is associated with an increase in PCa-specific mortality in carriers of the allele *G* [14]. There is evidence of a correlation of some polymorphic variants of the PI3K/PTEN/AKT pathway genes with the toxic effects of chemotherapy. For example, the association of the homozygous genotype rs2699887**GG* of gene *PIK3CA* with an increased risk of toxic effects in platinum-based therapy in patients with lung cancer is noted, while carriage of the rs2299939**C* allele in the *PTEN* gene, on the contrary, reduces the risk of serious side effects [15].

With regard to the important role of polymorphic variants of the gene components of the PTEN/PI3K/AKT signaling pathway in the formation of predisposition to various types of malignant tumors, the aim of this study was to search for associations of genotypes and alleles of polymorphic loci rs2494750 of the gene *AKT1*, rs2735343, rs2299941, and rs10490920 of the gene *PTEN*, rs17878362 of the gene *TP53*, and rs2699887 of the gene *PIK3CA* with a risk of developing prostate cancer.

MATERIALS AND METHODS

We used DNA samples isolated from the venous blood of patients with a histologically confirmed diagnosis of prostate cancer from the Republic of Bashkortostan, who are hospitalized at the Clinic of the Bashkir State Medical University. The sampling was carried out by the staff of the Department of Urology with the IPE course in accordance with the ethical standards of the bioethics committee, developed by the Declaration of Helsinki of the World Medical Association "Ethical Principles for Conducting Scientific Medical Research Involving Humans." Blood samples were obtained from all examined persons with their informed consent. The diagnosis was made on the basis of clinical and histological examination data.

The study included DNA samples from 394 patients with PCa and 342 healthy unrelated residents of the Republic of Bashkortostan who did not have malignant neoplasms, according to age, gender and ethnicity, and territorial residence corresponding to the group of patients. The mean age of the patients was 66.7 years (from 37 to 89 years at the time of diagnosis).

Genomic DNA was isolated from peripheral blood by phenol-chloroform extraction [16]. The concentration and purity of the isolated DNA were assessed by measuring the optical density using a NanoDrop ND-1000 spectrophotometer (Thermo Scientific). The genotypes of polymorphic loci were determined using the TaqMan allele discrimination method. Allelic discrimination analysis was performed using the CFX96 Real-Time PCR Detection System (BioRad). The results of each allelic discrimination were analyzed using CFX96 Real-Time PCR Detection System (BioRad) software.

Statistical Data Processing

Pairwise comparison of the frequencies of genotypes and alleles in groups of patients and healthy individuals in the study of polymorphic variants used the χ^2 criterion (p) for 2×2 contingency tables with Yates correction for continuity and SNPStats software. In the case of statistically significant differences, the strength of associations was assessed in terms of the odds ratio (OR); OR > 1 was considered as a positive association with an allele or genotype (high risk factor) and OR < 1 was considered as a negative association (low risk factor). The exponent of a single regression coefficient was interpreted as OR for the logistic model with the calculation of the 95% confidence interval (95%CI). All statistical tests were performed at a two-sided significance level; differences were considered statistically significant at p-value < 0.05, where p-value is the level of significance of the criterion.

RESULTS

On the basis of the published data, the study included the following polymorphic variants of the gene components of the PTEN/PI3K/AKT signaling pathway: rs2494750 of gene *AKT1*, rs2735343, rs2299941, rs10490920 of gene *PTEN*, rs17878362 of gene *TP53*, and rs2699887 of gene *PIK3CA*. Clinical and pathological characteristics of patients included in

Table 1. Clinical and pathological characteristics of prostate cancer patients and individuals in the control group

Indicator	Patients (n = 394)	Control (n = 342)
Age (mean ± SD), years	66.7 ± 0.37	58.7 ± 0.51
TNM stage, n (%)		–
I–II	201 (51.0)	–
III–IV	193 (49.0)	–
PSA level, n (%)		–
0.0–4.0	48 (12.2)	342 (100.0)
4.1–10.0	177 (45.0)	0
>10	169 (42.8)	0
Gleason index less than 8 points	287 (72.8)	–
Gleason index greater than 8 points	107 (27.2)	–
Histopathological characteristics of the tumor n (%)		–
Invasion of the seminal vesicles	49 (12.7)	–
Bilateral lesion of the prostate lobes	33 (9.4)	–

Table 2. Distribution of allele and genotype frequencies of the polymorphic locus rs2735343 of the gene *PTEN* in prostate cancer patients and controls

Genotypes, alleles	Patients		Control		χ^2	p-value	OR	95%CI
	n	pi ± Sp (95%CI)	n	pi ± Sp (95%CI)				
CC	37	9.64 ± 1.51 (6.88–13.04)	34	9.84 ± 1.61 (6.89–13.5)	0	0.9	0.96	0.59–1.57
CG	162	42.19 ± 2.52 (37.19–47.3)	118	34.43 ± 2.57 (29.39–39.73)	4.19	0.04	1.38	1.02–1.87
GG	185	48.18 ± 2.55 (43.08–53.3)	190	55.74 ± 2.69 (50.29–61.09)	3.65	0.05	0.74	0.55–0.99
C	236	31.68 ± 1.7 (28.35–35.15)	185	30.28 ± 1.86 (26.65–34.09)	0.25	0.59	1.06	0.84–1.34
G	509	68.32 ± 1.7 (64.85–71.65)	426	69.72 ± 1.86 (65.91–73.35)	0.25	0.59	0.93	0.74–1.18

Here and in Tables 3–5: OR—odds ratio, 95%CI—lower and upper limits of the 95% confidence interval for OR, p-value—level of significance of criterion.

the study and individuals in the control group are presented in Table 1. As a result of comparing the frequencies of alleles and genotypes between the general sample of patients with prostate cancer and the control group of healthy individuals, it was found that the genotype *CG* of polymorphic locus rs2735343 of gene *PTEN* associated with an increased risk of developing the disease (OR = 1.38, 95%CI = 1.02–1.87, p = 0.04), while the genotype *GG* showed a decrease in the frequency of occurrence in the group of patients compared with the control (OR = 0.74, 95%CI = 0.55–0.99, p = 0.05) (Table 2). When stratifying the group of patients with prostate cancer depending on histopathological characteristics, it was found that the rs2735343**C* allele was associated with an increased risk of bilateral damage to both lobes of the prostate and invasion of the seminal vesicles (Tables 3, 4).

As a result of the analysis of inheritance models using the SNPStats software, differences were revealed for the dominant and overdominant models of the polymorphic locus rs2735343 of the gene *PTEN* (Table 5). However, only for the overdominant model did the differences reach the established threshold of statistical significance p-value < 0.05. In both models, there is an association with an increased risk of developing PCa for the heterozygous genotype *CG*, suggest-

Table 3. Distribution of allele and genotype frequencies of the polymorphic locus rs2735343 of the gene *PTEN* in prostate cancer patients taking into consideration status of the lesion of both lobes of the prostate gland

Genotypes, alleles	There is bilateral involvement of both lobes		No bilateral involvement of both lobes		χ^2	*p*-value	OR	95%CI
	n	pi ± Sp (95%CI)	*n*	pi ± Sp (95%CI)				
CC	5	15.15 ± 6.24 (5.11–31.9)	32	9.12 ± 1.54 (6.32–12.63)	0.66	0.34	1.78	0.64–4.93
CG	18	54.55 ± 8.67 (36.35–71.89)	144	41.03 ± 2.63 (35.83–46.37)	1.74	0.14	1.72	0.84–3.53
GG	10	30.3 ± 8 (15.59–48.71)	175	49.86 ± 2.67 (44.5–55.21)	3.87	0.04	0.43	0.20–0.94
C	28	42.42 ± 6.08 (30.34–55.21)	208	29.63 ± 1.72 (26.27–33.16)	4.06	0.036	1.75	1.05–2.93
G	38	57.58 ± 6.08 (44.79–69.66)	494	70.37 ± 1.72 (66.84–73.73)	4.06	0.036	0.57	0.34–0.95

Table 4. Distribution of allele and genotype frequencies of the polymorphic locus rs2735343 of the gene *PTEN* in prostate cancer patients taking into consideration the invasion of the seminal vesicles

Genotypes, alleles	There is an invasion		No invasion		χ^2	*p*-value	OR	95%CI
	n	pi ± Sp (95%CI)	*n*	pi ± Sp (95%CI)				
CC	6	12.24 ± 4.68 (4.63–27.77)	31	9.25 ± 1.58 (6.37–12.88)	0.16	0.45	1.36	0.54–3.47
CG	27	55.1 ± 7.11 (40.23–69.33)	135	40.3 ± 2.68 (35–45.77)	3.25	0.06	1.81	0.99–3.32
GG	16	32.65 ± 6.7 (19.95–47.54)	169	50.45 ± 2.73 (44.96–55.93)	4.72	0.02	0.47	0.25–0.89
C	39	39.8 ± 4.94 (30.04–50.18)	197	29.4 ± 1.76 (25.98–33.01)	3.86	0.046	1.58	1.03–2.46
G	59	60.2 ± 4.94 (49.82–69.96)	473	70.6 ± 1.76 (66.99–74.02)	3.86	0.046	0.63	0.41–0.97

ing that the presence of both alternative alleles is necessary to modulate the risk of developing the disease.

Analysis of the frequency distribution of alleles and genotypes of polymorphic loci of the rs2494750 of gene *AKT1*, rs17878362 of gene *TP53*, and rs2699887 of gene *PIK3CA* in the groups of patients and in the control, taking into account ethnicity and clinical and pathological characteristics of the tumor, did not reveal statistically significant differences.

DISCUSSION

Prostate cancer is a heterogeneous disease with a lifetime detection rate of about 20% [17]. Despite the increase in the efficiency of diagnostic measures, the issue of identifying markers for early diagnosis of prostate cancer, as well as markers that can be used to classify tumors, assess their aggressiveness, and stratify patients for specific therapy, is still acute.

In the present study, polymorphic variants located in the genes that are components of the PTEN/PI3K/AKT signaling pathway were analyzed and associations were found for the polymorphic variant rs2735343 of the gene *PTEN* with a risk of developing prostate cancer.

The polymorphic variant rs2735343 of gene *PTEN* is located in the intron region and is able to influence splicing, protein expression, and, consequently, cell cycle regulation. Previously, it was shown that carriers of the homozygous genotype *GG* have a higher risk of

Table 5. Association of genotypes of the polymorphic variant rs2735343 of the gene *PTEN* with the risk of developing prostate cancer

Model	Genotype	Control	Patients	OR (95%CI)	*p*-value	AIC	BIC
Codominant	*G/G*	190 (55.6%)	185 (48.2%)	1.00	0.095	1005.3	1019.1
	C/G	118 (34.5%)	162 (42.2%)	1.41 (1.03–1.93)			
	C/C	34 (9.9%)	37 (9.6%)	1.12 (0.67–1.86)			
Dominant	*G/G*	190 (55.6%)	185 (48.2%)	1.00	0.047	1004.1	1013.2
	C/G-C/C	152 (44.4%)	199 (51.8%)	1.34 (1.00–1.80)			
Recessive	*G/G-C/G*	308 (90.1%)	347 (90.4%)	1.00	0.89	1008	1017.2
	C/C	34 (9.9%)	37 (9.6%)	0.97 (0.59–1.58)			
Superdominant	*G/G-C/C*	224 (65.5%)	222 (57.8%)	1.00	0.034	1003.5	1012.7
	C/G	118 (34.5%)	162 (42.2%)	1.39 (1.02–1.87)			
Log-additive	—	—	—	1.18 (0.94–1.47)	0.15	1006	1015.1

AIC—Akaike information criterion, BIC—Bayesian information criterion.

developing malignant tumors, including prostate cancer. The heterozygous genotype (*CG*) in these cases can create a nonfunctional protein, given that this tumor suppressor gene has very unusual characteristics. Unlike most tumor suppressor genes, the loss of only one allele results in an abnormal phenotype; i.e., it is considered a haploinsufficient suppressor and, as a result, does not follow the classical genetic model of biallelic inactivation [17]. Our study noted the association of the heterozygous genotype rs2735343**CG* with an increased risk of developing PCa, which may be due to the characteristic of the gene described above. Similar results were obtained in a study of breast cancer—the rs2735343 polymorphic variant showed an association with an increased risk of developing the disease in a codominant model [18]. It was also shown that the heterozygous genotype rs2735343**CG* was associated with an increased risk of esophageal squamous cell carcinoma [19]. The results of one of the studies based on a meta-analysis of data showed that the genotype *GG* of polymorphic locus rs2735343 is associated with an increased risk of cancer in Asian populations [20]. It was also previously found that the presence of the rs2735343**G* allele increases the risk of extracapsular extension, a condition that reduces the duration of the relapse-free period after prostatectomy in prostate cancer [17, 21]. In the present study, it was shown that the rs2735343**C* allele is associated with an increased risk of bilateral damage to both lobes of the prostate and invasion of the seminal vesicles, while the carriage of the homozygous rs2735343**GG* genotype was associated with a reduced risk of developing these pathological conditions.

Thus, despite the contradictory nature of the data obtained, it can be assumed that the polymorphic variant rs2735343 of the gene *PTEN* may be one of the molecular markers of the risk of developing PCa and some of the histopathological conditions of this disease. The results of this work can be used to create a panel of molecular markers for prognosis of the disease and assessment of tumor characteristics, nevertheless further validating studies are needed.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflicts of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in a study involving people comply with the ethical standards of the institutional and/or national committee for research ethics and the 1964 Helsinki Declaration and its subsequent changes or comparable ethical standards. Informed voluntary consent was obtained from each of the participants.

AUTHOR CONTRIBUTIONS

I.R. Gilyazova and E.A. Ivanova contributed equally to this work.

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