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Genetic research as a method for assessing susceptibility to prostate cancer

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The article presents the analyzes of literature sources describing the relationship between pathological alleles of some genes and prostate cancer, which can be used to determine the risk of developing prostate cancer. Mutations of the genes such as HOXB13 (251G/A, G84E), BRCA1 (5382insC, 185delAG, 4153delA, 3819delGTAAA, 3875delGTCT, 300T/G,2080delA) and BRCA2,CHEK2 (1100delC, I157T), ELAC2 (Leu217, Thr541, 650T, 1618a), cdh1 gene (160C/a), AR gene (CAG trinucleotide repeats), VDR gene (rs1544410, rs10875692, rs7301552, rs7975232, rs731236), GST family genes (null alleles of GSTM1 and GSTT1, single-nucleotide substitutions of GSTP1 313a/G and 341c/T), as well as Bloom's syndrome genes were studied. We described what mutations have a proven statistical association with an increased risk of prostate cancer. At the same time, the correlation between the patient's ethnicity and an increased risk of prostate cancer, when there are mutations of BRCA1, AR, VDR and GST family genes, is also noted.

Key words: prostate cancer; genetic research; gene-mutations

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Генетическое исследование как метод оценки предрасположенности к развитию рака предстательной железы

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В статье представлен анализы литературных источников, описывающих связь между патологическими аллелями некоторых генов и рака предстательной железы, которые, могут быть использованы в качестве определения риска развития рака предстательной железы. С этой целью оценивались патологические аллели таких генов, как ген HOXB13 (251G/A, G84E), ген BRCA1 (5382insC, 185delAG, 4153delA, 3819delGTAAA, 3875delGTCT,300T/G,2080delA) и BRCA2, ген CHEK2 (1100delC, I157T), ген ELAC2 (Leu217, Thr541, 650T, 1618A), ген CDH1 (160C/A), ген AR (тринуклеотидные повторы CAG), ген VDR (rs1544410, rs10875692, rs7301552, rs7975232, rs731236), гены семейства GST (нулевые аллели GSTM1 и GSTT1, однонуклеотидные замены гена GSTP1 313A/G и 341C/T), а так же гены синдрома Блума. Ряд онкогенов и патологических аллелей имеют доказанную статистическую связь с повышенным риском рака предстательной железы. При этом отмечается взаимосвязь этнической принадлежности и повышенного риска возникновения рака предстательной железы при наличии патологических аллелей таких генов, как ген BRCA1, ген AR, ген VDR и гены семейства GST.

Ключевые слова: рак предстательной железы; генетические исследования; мутации генов

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Introduction

Many oncological diseases are caused by dysregulation of the cell cycle due to dysfunction of regulator genes, which leads to uncontrolled cell division. The study of these mutations can be useful for calculating the risks of cancer pathogenic pathways, determining the degree of malignancy and tumour biological behaviour, assessing the metastatic potential, choosing a treatment method, and clarifying the effectiveness of therapy.

It is believed that the individual risk of carcinogenesis is determined by the individual susceptibility, which, in its turn, is determined by gene polymorphism that regulates the carcinogenic substance metabolism, cell cycle, inflammation, and many other key events of carcinogenesis and the risks of malignant tumours [1].

It is known that there are 6 – 14 key changes in the cell genome [2], while there may be thousands of tumour cell mutations. The key changes occur in signalling cellular pathways. Protein genes of signalling cascades are protooncogenes. More than 100 protooncogenes have been described, including *HER2/neu, EGFR, VEGFR, Bcl-2*, genes of the *RAS*, *RAF*, *Pi3K* family, and many others. There are also anti-oncogenes, or tumour suppressor genes, which include more than 20 representatives, the most famous of which are *ER, PR, Bax, P53, BRCA1/2*, etc.) [2].

Prostate cancer (PCa) is currently one of the most common cancers in the world. PCa is the most widespread one in the structure of oncological pathology in men In the USA and some European countries. More than 50% of patients visit a doctor having an already advanced disease in the T3 – T4 stage with metastases [3]. In the Russian Federation, the incidence of PCa was 93.7 per 100 000 in 2012, and almost every fifth tumour was diagnosed at stage 4 [4].

By 2015, the main genetic markers of PCa susceptibility were identified.

The *HOXB13* gene

The *HOXB13* gene is a regulator gene for other gene transcription. This being the case, the protein expressed with the *HOXB13* gene sequence is a transcription factor. The *HOXB13* protein belongs to a large group of transcription factors called the homeobox protein family. It acts as a tumour suppressor, which means that it interferes with rapid and uncontrolled cell growth and division. Members of the *HOXB* gene group are expressed in the posterior part of an embryo including the developing genitourinary system. The *HOXB13* gene transcripts are widely represented in the human prostate tissue [5]. In 2009, the study concluded that this gene plays a role in the normal development of the prostate gland by affecting the DNA-binding transcription domain of androgen receptors [6].

Many studies have been carried out to investigate the mutation of this gene, for example, *251G/A (rs138213197)* pathogenic allele, which was most often found in patients with early onset of the disease and hereditary background [7]. *G84E* pathogenic allele of the *HOXB13* gene possesses the same characteristics [6]. Also, in 2015, a study was conducted where almost 30% of patients had overexpression of the *HOXB13* gene, which is directly related to the activity of androgen receptors [8]. C.K. Park et al. conducted studies proving the relationship between overexpression of the *HOXB13* gene with a higher Gleason score, disease stage and biochemical relapse occurrence [9], which demonstrates the significance of the *HOXB13* gene determination in predicting PCa.

The *BRCA1* gene

The *BRCA1* gene encodes a protein that is also a tumour suppressor. The *BRCA1* protein is involved in the repair of damaged DNA, restoring DNA breaks through homologous recombination [5]. The *BRCA1* protein plays an important role in maintaining the stability of the cell's genetic information by participating in DNA repair synthesis.

There are many mutations in the *BRCA1* gene that are associated not only with PCa, but also with breast cancer, ovarian cancer, pancreatic cancer, and other kinds of it [10]. Patients have *BRCA1* germline mutations in PCa diagnostics usually have higher Gleason scores ≥8, T3/T4 stage of the disease, metastases availability, and a relatively early onset of the disease [11].

The most frequent pathogenic alleles found in the Russian population are *5382insC, 185delAG, 4153delA, 3819delGTAAA, 3875delGTCT, 300T/G, 2080delA* [5]. In the Republic of Bashkortostan, an analysis of pathogenic alleles of the *BRCA1* gene was carried out, which showed an increased frequency of *5382insC* mutation carriage among patients diagnosed with PCa [12]. At the same time, the study of this pathogenic allele of the BRCA1 gene was carried out in Novosibirsk, as a result of which the 5382insC mutation was not found in any of the patients with PCa [13], which may be due to the ethnic characteristics of patients in different groups. In the study conducted in the Republic of Bashkortostan, both patients with the pathogenic allele were ethnic Russians, and in the study conducted in Novosibirsk, ethnicity was not indicated.

The *BRCA2* gene

The *BRCA2* gene has the same characteristics as the *BRCA1* gene but it is noted that the carriage of pathogenic alleles of the *BRCA2* gene is more critical for the prostate carcinogenesis than the carriage of pathogenic alleles of the *BRCA1* gene. The IMPACT study demonstrated that the frequency of detecting PCa of intermediate and high risk in these subgroups was higher than in individuals without the pathogenic alleles carriage. Herewith, prognostically unfavourable tumours were detected in 2.3% of patients with pathogenic alleles of the BRCA1 gene and 3.3% of patients with pathogenic alleles of the *BRCA2* gene [14].

The *CHEK2* gene

The *CHEK2* gene encodes a protein kinase that blocks cell division in G1 phase. This protein inhibits the work of *CDC25C* phosphatase, as a result of which the cell does not enter mitosis. Protein kinase interacts with the *BRCA1* gene protein involved in DNA repair synthesis and stabilizes the *p53* gene protein [5]. Pathogenic alleles of this gene are associated with the thyroid, colon, and breast cancers [15]. Back in 2003, X. Dong et al. determined the possibility of a direct relationship between *CHEK2* gene mutations and PCa [16]. Other studies have identified a direct relationship between cytidine deletion at *1100 (1100delC)* position and the replacement of isoleucine for threonine at *157 (I157T)* nucleotide and the risk of prostate carcinogenesis [17].

The *ELAC2* gene

The *ELAC2* gene encodes a ribonuclease that removes the 3'-end from the *tRNA* precursor. This protein interacts with *SMAD2*, which interacts with transforming growth factor-beta *(TGFb)* and thereby regulates cell growth and division. S.V. Tavtigian et al. [18] did not confirm the relationship between the carriage of the *Leu217* allele and the risk of prostate carcinogenesis in a 2001 study. In 2002, Nicola J. Camp and Sean V. Tavtigian proved the relationship between the carriage of the pathogenic *Thr541* allele of the *ELAC2* gene separately or in combination with the *Leu217* allele and the risk of prostate carcinogenesis [19]. At the same time, a new study was conducted in 2019, which confirmed a high-risk availability of PCa in patients with the *Leu217* allele. It was established the risk is higher with the carriage of two Leu21 alleles in comparison with the heterozygous variant (OR = 6.080 and 1.030, respectively) in residents of the Republic of Cameroon [20], which indicates a possible lack of studies of this mutation before. Also, concerning the carriage of the *Leu217* and *Thr541* alleles, it is known that the carriage of the 650T and *1618A* alleles of the *ELAC2* gene increases the risk of prostate carcinogenesis [(OR = 1.13 and 1.22, respectively).

The *CDH1* gene

The *CDH1* gene encodes epithelial cadherin or E-cadherin, which is located on the epithelial cell membranes and is involved in cell adhesion. Also, E-cadherin is involved in signal transduction in the cells, regulates cell growth, maturation and movement. E-cadherin dysfunction plays a role in malignant tumour metastasis [5]. This is due to the ability of cells to avoid "anoikis" (one of the apoptosis pathways that occurs in response to impaired cell adhesion, or a complete loss of the ability of cells to adhere) with the loss of E-cadherin. The most studied single nucleotide substitution is *160C/A* and the availability of A allele in homozygous or heterozygous variants increases the risk of developing PCa in comparison with the homozygous C/C genotype [21, 22].

The *AR* gene

The AR gene encodes a receptor against androgen. A feature of this gene is the availability of triplet or trinucleotide *CAG* nucleotide repeats, which normally ranges from 10 to 36. A meta-analysis was carried out, proving that the number of *CAG* triplets less than 20 is associated with a higher risk of PCa [23]. There is also an ethnic feature of this gene polymorphism: African Americans, on average, have a smaller number of *CAG* triplets, which may indicate a higher risk of developing PCa in African Americans [24].

The *VDR* gene

The *VDR* gene encodes a receptor against vitamin D. Back in 1992, G.J. Miller et al. in an experiment with the *LNCaP* cell line proved that calcitriol stimulates the differentiation of prostate cells [25]. Many polymorphisms of the *VDR* gene have been studied, which are associated with a high risk of developing PCa, for example, *rs1544410*, *rs10875692*, *rs7301552*, *rs7975232*, *rs731236* [26, 27, 28]. At the same time, ambiguous results are showing that African Americans do not have a relationship between the carriage of the *rs1544410* mutation and a high risk of developing PCa [28]. The absence of relationships between the *rs2228570* (*FokI*) and *rs2238135* substitutions in the *VDR* gene and the risk of developing PCa in the West Siberian region of Russia were also noted [29].

The *GST* family genes

The *GST* family genes encode various types of glutathione-S-transferases that catalyze the conjugation of reduced glutathione with various hydrophobic compounds and are phase II enzymes for xenobiotic detoxification [5]. The polymorphism of this gene is due to the availability or absence of a deletion, which leads to a violation of the synthesis of the glutathione-S-transferase protein. In this case, the gene in which there is a deletion is referred to as the "null allele" [5]. Numerous studies have shown a link between the availability of a null allele and the risk of developing PCa. Dajun Liu et al. conducted a systematic review and meta-analysis and concluded that the availability of the *GSTM1* null allele and *GSTT1* significantly increased the risk of PCa in Asians, with the availability of a "double null allele" associated with a higher risk of developing PCa [30]. In the Algerian population, an association between the availability of the *GSTM1* gene null allele and the risk of developing PCa was also noted. However, the availability of a significant relationship between the risk of developing PCa and the carriage of the *GSTM1* gene null allele among the Algerian population has not been confirmed. [31]. The *GSTP1* gene polymorphism is associated with the availability of two single nucleotide substitutions, *313A/G* (*I105V, rs1695*) and 341C/T (*A114V*, *rs1138272*) [32]. An association was found between the carriage of the *GSTP1* gene *341C/T* polymorphism and the risk of developing cancer, including PCa, which may be associated with a decrease in detoxification activity [33]. The availability of *313A*/G polymorphism is associated with the risk of PCa, not in all ethnic groups (Caucasians have this relationship, but Asians and African Americans do not) [34].

The Bloom syndrome gene

The possible connection between mutations in the Bloom syndrome gene and the risk of developing PCa was also studied. This gene encodes RecQ helicase, which is involved in DNA repair synthesis and maintaining genome stability. Previously, an association was established between heterozygous carriage of the Bloom gene mutations and breast cancer, but the link was not found between the carriage of the Bloom gene mutations and the risk of prostate carcinogenesis [35].

Conclusion

This literature review highlights only a subset of the genetic mutations associated with an increased risk of PCa. Undoubtedly, there is a hereditary susceptibility to PCa, and this important issue requires even more research. There is no doubt that the popularization of genetic screening is possible, especially in families with cases of PCa, ovarian cancer and breast cancer. So, L. Davenport published an article "Men with the *BRCA2* gene pathogenic alleles carriage should be examined for PCa" in 2019, in which he proved both an increased incidence of PCa in carriers of the *BRCA2* gene pathogenic alleles and a high prognostic value of the positive biopsy result (31% among carriers versus 18% among non-carriers) [36]. On the other hand, these mutations are rare among patients with PCa, which means they cannot be used as the only method for assessing the risk of prostate malignant tumour growth. It is also important to continue research on the relationship between the mutation and the ethnicity of the patient, and the role of this mutation in the prostate carcinogenesis in different populations.

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