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# THE ROLE OF THE POLYMORPHIC LOCUS ILE157THR OF THE CHEK2 GENE IN THE DEVELOPMENT OF PROSTATE CANCER

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**Abstract**

**The aim of the study** was to investigate the influence of the Ile157Thr polymorphic locus of the CHEK2 gene on the development of prostate cancer.

**Materials and Methods.** The study included a total of 197 blood samples, 90 of which were randomly selected from apparently healthy men aged 45–72 years, 42 from patients with benign prostatic hyperplasia, and 65 from patients with prostate cancer. All samples were obtained from residents of the Andijan region. The resulting blood samples were tested for the presence of the Ile157Thr polymorphism of the CHEK2 gene using allele-specific PCR in the clinical laboratory of the Republican Specialized Scientific and Practical Medical Center of Hematology. The obtained results were analyzed in accordance with the Hardy-Weinberg equilibrium.

**Results**. The observed and expected allele and genotype frequencies of the Ile157Thr polymorphism in the CHEK2 gene according to the Hardy-Weinberg equilibrium showed that the Ile and Thr allele frequencies among the main group of patients were 0.97 and 0.03, respectively. The homozygous Thr/Thr genotype was not detected in any of the groups. The differences between the actual distribution and the expected values of the homozygous Ile/Ile genotype in the comparison group were insignificant and completely consistent with each other (0.99 and 0.99; $\chi^2$=0.0; p=0.9). It was found that the prevalence of heterozygous Ile/Thr genotypes of the specified polymorphic locus was higher in patients of

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the main group (5.6%) than in samples of the control group (1.1%), but no statistically significant differences were found between the study groups ($\chi^2$=2.9; P=0.1).

**Keywords**: prostate cancer screening, CHEK2 gene Ile157Thr polymorphism, prostate cancer development, aggressive prostate cancer

## Introduction

**Relevance of the problem.** Prostate cancer (PC) is a classic example of an oncological disease with pronounced clinicopathological heterogeneity. This means that a single term covers a spectrum of diseases with radically different biological behavior, prognosis, and treatment approaches [3]. Understanding this heterogeneity is a central challenge in modern oncology, as it is directly related to two major problems: on the one hand, the overdiagnosis and treatment of clinically insignificant tumors, and on the other hand, the need for timely and aggressive treatment of life-threatening forms [1]. The diagnosis and prognostic stratification of prostate cancer is traditionally based on three pillars: serum prostate-specific antigen (PSA) levels, clinical stage according to the TNM system, and biopsy-based Gleason score [2]. Despite their widespread use and inclusion in international guidelines, these tools have significant limitations that lead to problems of overdiagnosis, overtreatment, and in some cases, underestimation of the aggressiveness of the disease [5]. In modern oncology, there is a need to integrate new, more accurate biomarkers for a personalized approach to patients [4].

## Materials and Methods

A total of 197 blood samples were studied in the study, 90 of which were randomly selected from conditionally healthy men aged 45-72, 42 patients with benign prostatic hyperplasia, and 65 patients with prostate cancer. All samples

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were collected from the population of Andijan region. The obtained blood samples were tested for the Ile157Thr polymorphic locus of the SHEK2 gene by allele-specific PCR in the clinical laboratory department of the Republican Specialized Scientific and Practical Medical Center of Hematology. The results obtained were analyzed according to Hardy-Weinberg equilibrium.

**Results and Discussions**

The distribution of alleles and genotypes of the Ile157Thr polymorphic marker in the CHEK2 gene in the main and control groups corresponded to the expected results according to the Hardy-Weinberg law (HWQ) ($r<0.05$). The frequencies of the Ile and Thr alleles among the main group of patients were 0.97 and 0.03 (Table 1). At the same time, the observed distribution of the wild homozygous Ile/Ile genotype detected in the patient group was consistent with the expected values (0.94 and 0.94, respectively; $\chi2=0.0$; $r=0.7$).

It was also noted that the observed results of the unfavorable heterozygous Ile/Thr genotype were statistically insignificantly higher than expected ($\chi2=0.0$; $r=0.7$; 0.06 and 0.05). The Thr/Thr homozygous genotype was not detected in either group (Table 1).

The relative deviation of Hobs and Hexp among the patients in the main group was positive and amounted to D= 003.

In the control group, the observed and expected genotype frequencies were the same, and no statistically significant differences were detected between them (Table 2).

The results obtained within the framework of the study showed that the distribution of major Ile and minor Thr alleles among conditionally healthy individuals was 0.99/ 0.01, respectively.

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**Table 1 Distribution of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene according to Hardy-Weinberg equilibrium in the main group.**

| Main group | | | | | |
|---|---|---|---|---|---|
| Alleles | Allele frequency | | | | |
| Ile | 0.97 | | | | |
| Thr | 0.03 | | | | |
| Genotypes | Genotype frequency | | $\chi^2$ | p | df |
| | Observed | Expected | | | |
| Ile/Ile | 0.94 | 0.94 | 0 | | |
| Ile/Thr | 0.06 | 0.05 | 0 | | |
| Thr/Thr | 0 | 0 | 0.08 | | |
| Total | 1 | 1 | 0.09 | 0.7 | 1 |

Among the patients in the main group, the relative deviation of Hobs and Hexp was positive and amounted to D= 003.

In the control group, the observed and expected genotype frequencies were the same, and no statistically significant differences were detected between them (Table 2).

The results obtained within the framework of the study showed that among conditionally healthy individuals, the distribution of major Ile and minor Thr alleles was 0.99/ 0.01, respectively.

**Table 2** Distribution of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene according to Hardy-Weinberg equilibrium in the comparison group.

| Comparison group | | | | | |
|---|---|---|---|---|---|
| Alleles | Allele frequency | | | | |
| Ile | 0.99 | | | | |
| Thr | 0.01 | | | | |
| Genotypes | Genotype frequency | | $\chi^2$ | p | df |
| | Observed | Expected | | | |
| Ile/Ile | 0.99 | 0.99 | 0 | | |
| Ile/Thr | 0.01 | 0.01 | 0 | | |
| Thr/Thr | 0 | 0 | 0 | | |
| Total | 1 | 1 | 0 | 0.9 | 1 |

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According to Table 2, the differences between the actual distribution of the homozygous Ile/Ile genotype and the expected values in the comparison group were insignificant and fully consistent with each other (0.99 and 0.99; $\chi 2=0.0$; $r=0.9$). At the same time, the observed frequency of the heterozygous Ile/Thr genotype was also completely consistent with the expected results and the differences between them were found to be statistically insignificant (0.01 and 0.01; $\chi 2=0.0$; $r=0.9$). The unfavorable homozygous Thr/Thr genotype was not recorded among the control group, as well as among the patients in the main group.

In the control group, the number of (Hobs) was the same as the expected values, and accordingly, D= 0.01 was shown.

Thus, the molecular genetic results obtained for the Ile157Thr polymorphic locus in the CHEK2 gene were representative and did not deviate from Hardy-Weinberg equilibrium ($\chi 2<3.84$, $r>0.05$).

According to the results of a comparative analysis of the prevalence of alleles and genotypes of the Ile157Thr polymorphic marker in the CHEK2 gene in the patients who made up the main group and the control group, the frequency of the minor Thr allele was characterized by a non-significant difference between the two groups (2.8% versus 0.6%; $\chi 2=2.8$ $r=0.1$) (Table 3).

**Table 3** Comparative analysis of the prevalence of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene in the main group and comparison group samples.

| Alleles and genotypes | Amount of alleles and genotypes tested | | | | $\chi 2$ | p | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Main group | | Comparison group | | | | | |
| | n | % | n | % | | | | |
| Ile | 208 | 97.2 | 179 | 99.4 | 2.8 | 0.10 | 0.2 | 0.03 - 1.31 |
| Thr | 6 | 2.8 | 1 | 0.6 | 2.8 | 0.10 | 5.2 | 0.76 - 34.94 |
| Ile/Ile | 101 | 94.4 | 89 | 98.9 | 2.9 | 0.10 | 0.2 | 0.03 - 1.29 |
| Ile/Thr | 6 | 5.6 | 1 | 1.1 | 2.9 | 0.10 | 5.3 | 0.77 - 36.14 |

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It was found that the prevalence of heterozygous Ile/Thr genotypes of the above polymorphic locus was higher in patients in the main group (5.6%) than in samples from the control group (1.1%), but no statistically significant differences were found between the groups under study ($\chi 2=2.9$; R=0.1) (Figure 1).

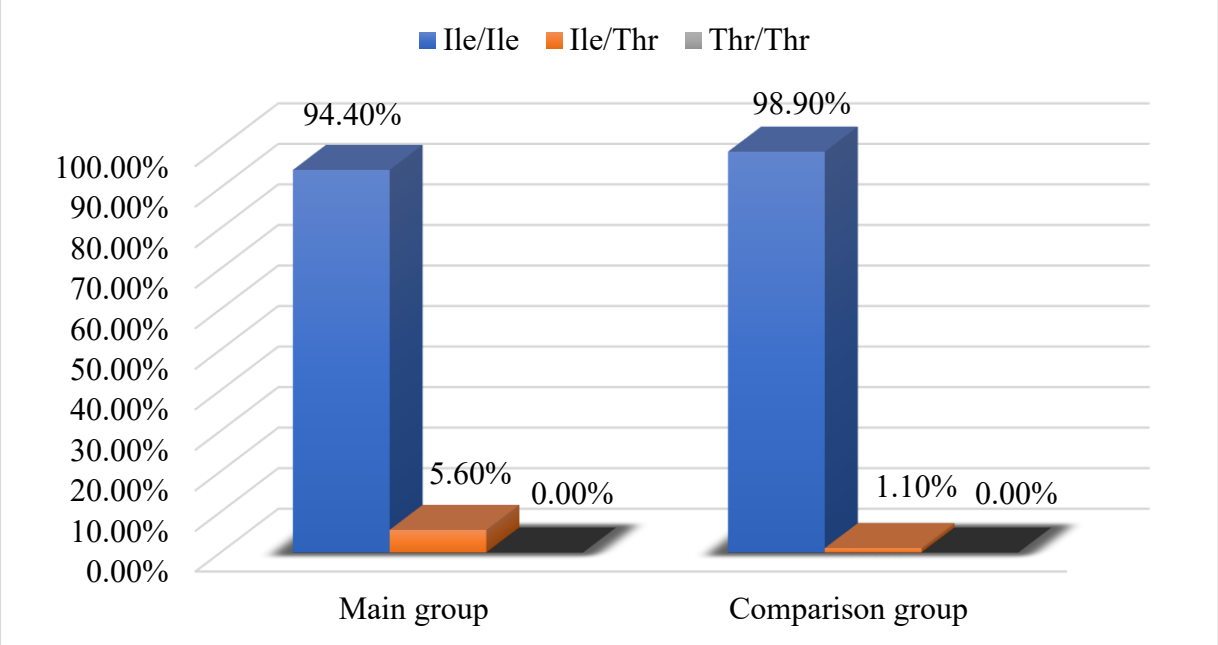


**Figure 1. Comparative analysis of the prevalence of alleles and genotypes of the CHEK2 gene Ile157Thr polymorphism in the main group of patients and comparison group samples.**

However, despite the statistically insignificant differences, the incidence of minor Thr and heterozygous Ile/Thr genotypes in the main group of patients was higher than in the reference group, indicating a tendency for carriers of these alleles and genotypes to have an increased risk of developing these diseases. Also, according to the results of the analysis, it was found that the probability of developing prostate cancer in patients with these alleles and genotypes was 5.2 and 5.3 times

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higher than in the comparison group, respectively (OR=5.2; 95%CI:0.76-34.94 and OR=5.3; 95%CI:0.77–36.14) (Table 3).

According to the analysis of the data presented in Figure 3.1, the Ile157Thr polymorphism in the CHEK2 gene was significantly less likely to cause functionally active Ile/Ile homozygous genotype in the main group of patients.

In particular, this genotype was detected in 101 out of 107 patients in the main group (94.4%), while in 89 out of 90 healthy individuals (98.9%). However, these differences were not statistically significant ($\chi2<3.84$; $r>0.05$). Also, the frequency of the major Ile allele in the main group of patients was slightly lower than in the comparison group (97.2%), while in the group of relatively healthy individuals this indicator was 99.4%, respectively ($\chi2=2.8$;$r=0.1$; OR=0.2; 95%CI:0.03 - 1.31) (Table 3).

Within the framework of the study, differences in the frequency of alleles and genotypes of the above genetic marker were also studied among subgroups of patients with prostate cancer and benign prostatic hyperplasia, which constituted the main group, according to the case-control design.

The results of the analysis of the frequency of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene in the study groups are presented in Table 4. According to the results of the analysis, the frequency of the wild Ile allele among patients with prostate cancer was 96.2%, which was slightly lower than in the group of patients with benign prostatic hyperplasia, in which the wild Ile allele was observed in 98.8% of cases ($\chi2=1.3$; R=0.3; OR=0.3; 95%CI:0.04-2.33). However, the null Thr allele, on the contrary, was found to be significantly more common in the group of patients with prostate cancer than in the group with prostate adenoma (3.8% versus 1.2%; $\chi2=1.3$; R=0.3; OR=3.3; 95%CI:0.43-25.7). However, analysis of the results showed that no statistically significant differences were detected in the frequency of the above alleles between the groups ($\chi2>3.84$; $r<0.05$) (Table 4).

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When analyzing the frequency of genotypes in the studied groups, it was found that the wild-type homozygous Ile/Ile genotype was the most common form in both groups. In particular, this genotype was detected in 92.3% of cases in the group of patients with prostate cancer and in 97.6% of cases in the group of patients with benign prostatic hyperplasia ($\chi2$=1.4; r=0.3; OR=0.3; 95%CI:0.04-2.31) (Table 4). On the contrary, the unfavorable heterozygous Ile/Thr genotype was recorded in the least cases among the participants in both groups (7.7% versus 2.4%; $\chi2$=1.4; r=0.3; OR=0.3; 95%CI:0.04-2.31). The differences in the frequency of occurrence of wild-type Ile/Ile and heterozygous Ile/Thr genotypes in the study groups were not statistically significant (r>0.05) (Table 4).

**Table 4** Comparative analysis of the prevalence of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene in samples from a group of patients with prostate cancer and benign prostatic hyperplasia.

| Alleles and genotypes | Amount of alleles and genotypes tested | | | | $\chi2$ | p | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Prostate cancer n=65 | | Benign prostatic hyperplasia n=42 | | | | | |
| | n | % | n | % | | | | |
| Ile | 125 | 96.2 | 83 | 98.8 | 1.3 | 0.30 | 0.3 | 0.04 - 2.33 |
| Thr | 5 | 3.8 | 1 | 1.2 | 1.3 | 0.30 | 3.3 | 0.43 - 25.7 |
| Ile/Ile | 60 | 92.3 | 41 | 97.6 | 1.4 | 0.30 | 0.3 | 0.04 - 2.31 |
| Ile/Thr | 5 | 7.7 | 1 | 2.4 | 1.4 | 0.30 | 3.4 | 0.43 - 26.94 |

During the study, none of the patients with prostate cancer or benign hyperplasia had a negative Thr/Thr genotype.

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A significant 7.2-fold increase in the incidence of the adverse Thr allele in patients with prostate cancer compared to the control group (3.8% vs. 0.6%; $\chi2$=4.3; r=0.05; OR=7.2; 95%CI:1.12-45.96) confirms the association of this allele with an increased risk of developing this pathology. On the contrary, a significant decrease in the wild-type Ile allele in the above group of patients indicates a potential protective effect against the development of prostate cancer (96.2% vs. 99.4%; $\chi2$=4.3; r=0.05; OR=0.1; 95%CI:0.02-0.9) (Table 5).

**Table 5** Comparative analysis of the prevalence of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene in prostate cancer and control group samples.

| Alleles and genotypes | Amount of alleles and genotypes tested | | | | $\chi2$ | p | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Prostate cancer | | Benign prostatic hyperplasia | | | | | |
| | n | % | n | % | | | | |
| Ile | 125 | 96.2 | 179 | 99.4 | 4.3 | 0.05 | 0.1 | 0.02 - 0.9 |
| Thr | 5 | 3.8 | 1 | 0.6 | 4.3 | 0.05 | 7.2 | 1.12 - 45.96 |
| Ile/Ile | 60 | 92.3 | 89 | 98.9 | 4.4 | 0.05 | 0.1 | 0.02 - 0.88 |
| Ile/Thr | 5 | 7.7 | 1 | 1.1 | 4.4 | 0.05 | 7.4 | 1.14 - 48.3 |

The results of the genotype distribution analysis showed that the Ile/Ile homozygous wild genotype was a protective factor that reduced the risk of developing prostate cancer (92.3% vs. 98.9%; $\chi2$=4.4; r=0.05; OR=0.1 95%CI:0.02-0.88) (Figure 2). The Ile/Thr negative heterozygous genotype was also found to have a provocateur effect on the development of the disease (7.7% vs. 1.1; $\chi2$=4.4; r=0.05; OR=7.4 95%CI:1.14-48.3). In other words, the probability of developing prostate cancer in individuals with the above heterozygous genotype was 7.4 times higher than in individuals without this genotype (Table 5).

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Comparative analysis of the allele frequencies of the Ile157Thr polymorphism in the CHEK2 gene in samples from patients with benign prostatic hyperplasia (BPH) and controls showed that the proportion of the wild-type Ile allele in the patient group was 98.8%, which was slightly lower than in the control group (99.4%), and there were no statistically significant differences (χ2=0.3; r=0.6; OR=0.5; 95%CI:0.03-7.03). At the same time, the negative Thr allele was detected in 1.2% of patients with BPH, which was slightly higher than 0.6% in the reference group, but the difference between the groups was not statistically significant. (ch2=0.3? r=0.6; OR=2.2; 95%CI:0.14-32.68) (Table 6).

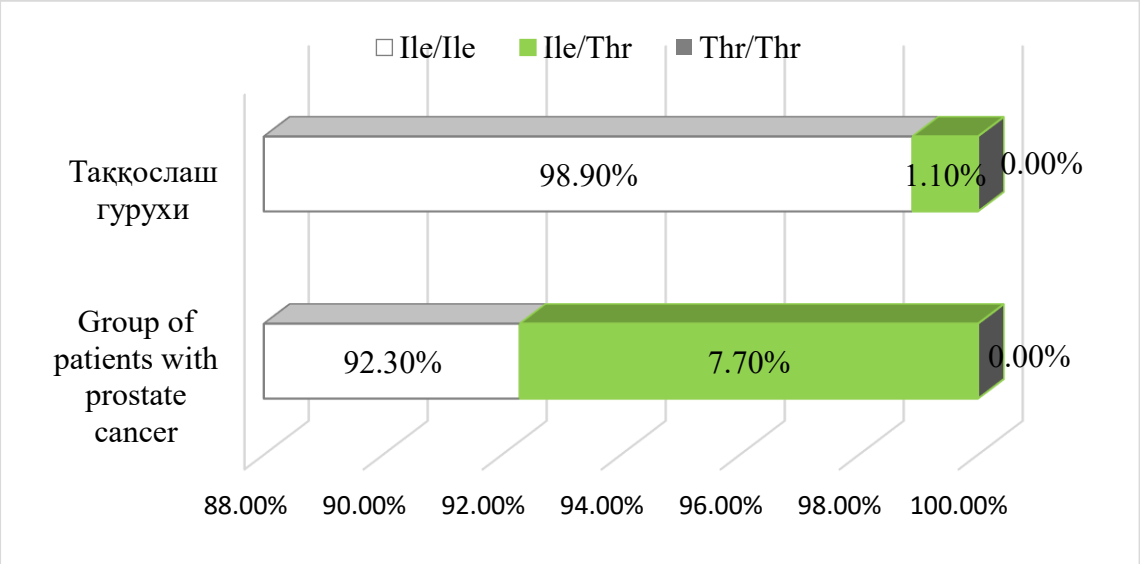


**Figure 2. Comparative analysis of the prevalence of alleles and genotypes of the CHEK2 gene Ile157Thr polymorphism in patients with prostate cancer and comparison group samples.**

At the same time, the frequency of the wild-type homozygous Ile/Ile genotype in the group of patients with PBXGP was slightly lower than in the control group, being 97.6% versus 98.9%, respectively (χ2=0.3; r=0.6; OR=0.5; 95%CI:0.03-7.07) (Table 6).

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The results of the probabilistic analysis of the heterozygous Ile/Thr genotype in the development of PBXGP showed that this genotype was recorded in 2.4% of cases in the group of patients. Although the calculated hazard ratio (OR) was equal to 2.2, the difference did not reach statistical significance compared to the indicator in the group of conditionally healthy individuals (1.1%) ($\chi^2 = 0.3$; p=0.6; 95% CI:0.14-33.31) (Table 6).

**Table 6 Comparative analysis of the prevalence of alleles and genotypes of the Ile157Thr polymorphism in the CHEK2 gene in benign prostatic hyperplasia and comparison group samples.**

| Alleles and genotypes | Amount of alleles and genotypes tested | | | | χ2 | p | OR | 95%CI |
|---|---|---|---|---|---|---|---|---|
| | Benign prostatic hyperplasia | | Comparison group | | | | | |
| | n | % | n | % | | | | |
| Ile | 83 | 98.8 | 179 | 99.4 | 0.3 | 0.60 | 0.5 | 0.03 - 7.03 |
| Thr | 1 | 1.2 | 1 | 0.6 | 0.3 | 0.60 | 2.2 | 0.14 - 32.68 |
| Ile/Ile | 41 | 97.6 | 89 | 98.9 | 0.3 | 0.60 | 0.5 | 0.03 - 7.07 |
| Ile/Thr | 1 | 2.4 | 1 | 1.1 | 0.3 | 0.60 | 2.2 | 0.14 - 33.31 |

**In conclusion,** it was found that the frequency of the Thr negative allele of the SHEK2 gene Ile157Thr genetic marker in patients with prostate cancer was significantly higher than in the control group. In particular, in the group of patients with PBS, it was 3.8%, while in the control group, this indicator was only 0.6% (χ2=4.3; r=0.05; OR=7.2; 95%CI:1.12-45.96). In other words, such a difference in the occurrence of the Thr allele in the PBS group compared to the responders group confirms that it is associated with a higher risk of developing this pathology. On the contrary, in the above group of patients, a significant

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decrease in the frequency of the wild-type Ile allele was observed (99.4% versus 96.2%; $\chi 2=4.3$; r=0.05; OR=0.1; 95%CI:0.02-0.9). This suggests that this allele has a certain protective effect against the development of prostate cancer.

Genotype analysis also showed this trend. The results of the genotype distribution analysis showed that the Ile/Ile homozygous wild genotype was a protective factor that reduced the risk of developing prostate cancer (92.3% vs. 98.9%; $\chi 2=4.4$; r=0.05; OR=0.1 95%CI:0.02-0.88). The Ile/Thr negative heterozygous genotype was also found to have a provocateur effect on the development of the disease (7.7% vs. 1.1; $\chi 2=4.4$; r=0.05; OR=7.4 95%CI:1.14-48.3). In other words, the probability of developing prostate cancer in individuals with the above heterozygous genotype was 7.4 times higher than in individuals without this genotype.

Thus, the data obtained allow us to evaluate the Ile157Thr polymorphic locus of the SHEK2 gene as an important molecular-genetic marker affecting the development of prostate cancer, and is of great importance in early prediction of the development of PBS in a group of patients with a hereditary predisposition and in the formation of individual preventive measures.

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