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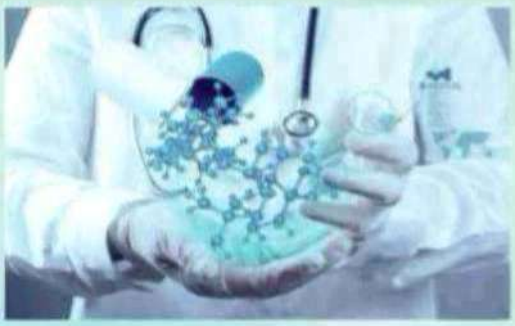

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THE ROLE OF THE G2014A/THR594THR POLYMORPHISM IN THE ESR1 GENE IN THE PATHOGENESIS OF BENIGN PROSTATIC HYPERPLASIA AND PROSTATE CANCER

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✓ ***Resume***

This thesis investigates the role of the G2014A/Thr594Thr polymorphism in the ESR1 gene in the development of Benign Prostatic Hyperplasia (BPH) and Prostate Cancer (PC). The ESR1 gene encodes the estrogen receptor alpha (ERα), which plays a critical role in the regulation of cellular processes influenced by estrogen signaling. The G2014A polymorphism results in the Thr594Thr substitution, a variation that may affect receptor function and, consequently, influence prostate tissue growth and disease progression. The research explores whether this genetic variation contributes to the pathogenesis of BPH, a non-cancerous enlargement of the prostate, and PCa, a hormone-dependent malignancy. The study will also examine potential molecular mechanisms through which the polymorphism alters estrogen receptor activity and its effects on prostate cell proliferation, apoptosis, and androgen receptor signaling. By clarifying the role of this polymorphism, the thesis aims to provide insights into the genetic underpinnings of prostate diseases, with potential implications for risk assessment, early detection, and targeted therapies.

Keywords: Benign Prostatic Hyperplasia (BPH), prostate cancer, genetic polymorphisms, ESR1 gene, G2014A/Thr594Thr Polymorphism.

РОЛЬ ПОЛИМОРФИЗМА G2014A/THR594THR В ГЕНЕ ESR1 В ПАТОГЕНЕЗЕ ДОБРОКАЧЕСТВЕННОЙ ГИПЕРПЛАЗИИ ПРЕДСТАТЕЛЬНОЙ ЖЕЛЕЗЫ И РАКА ПРОСТАТЫ

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✓ ***Резюме***

Данное исследование посвящено изучению роли полиморфизма G2014A/Thr594Thr в гене ESR1 в развитии доброкачественной гиперплазии предстательной железы (ДГПЖ) и рака простаты (РП). Ген ESR1 кодирует эстрогеновый рецептор альфа (ERα), который играет важную роль в регуляции клеточных процессов, опосредованных эстрогенной сигнализацией. Полиморфизм G2014A приводит к замене Thr594Thr, которая может повлиять на функцию рецептора и, как следствие, на рост тканей простаты и прогрессирование заболеваний. Исследование направлено на выявление связи данной генетической вариации с патогенезом ДГПЖ, неонкологического увеличения простаты, и РП, гормонозависимой злокачественной опухоли. Кроме того, изучаются молекулярные механизмы, посредством которых этот полиморфизм изменяет активность эстрогенового рецептора и его влияние на пролиферацию клеток предстательной железы, апоптоз и андрогеновую сигнализацию. Прояснение роли данного полиморфизма может способствовать лучшему пониманию генетических основ заболеваний простаты, что потенциально полезно для оценки рисков, ранней диагностики и разработки целевых методов терапии.

Ключевые слова: Доброкачественная гиперплазия предстательной железы (ДГПЖ), рак простаты, генетические полиморфизмы, ген ESR1, полиморфизм G2014A/Thr594Thr.

ESR1 GENINING G2014A/THR594THR POLIMORFIZMINING PROSTATA BEZINING HAVFSIZ GIPERPLAZIYASI VA PROSTATA RAKI PATOGENEZIDAGI ROLI

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✓ ***Rezume***

Ushbu tadqiqot ESR1 genining G2014A/Thr594Thr polimorfizmining prostata bezi xavfsiz giperplaziyasi (PBXG) va prostata bezi saratoni (PBS) rivojlanishidagi rolini o‘rganishga bag‘ishlangan. ESR1 geni estrogen retseptori alfa (ERα)ni kodlaydi, u estrogen signalizatsiyasi ta’siridagi hujayraviy jarayonlarning tartibga solinishida muhim rol o‘ynaydi. G2014A polimorfizmi Thr594Thr o‘rin almashishini keltirib chiqaradi, bu esa retseptor faoliyatiga ta’sir qilishi va natijada prostata to‘qimalarining o‘sishi hamda kasalliklar progressiyasiga ta’sir ko‘rsatishi mumkin. Tadqiqot ushbu genetik variatsiya PBXG – prostatning xavfsiz giperplaziyasi va PBS – gormonga bog‘liq rak patogeneziga qanday ta’sir qilishini aniqlashga qaratilgan. Shuningdek, mazkur polimorfizm estrogen retseptorining faoliyatini qanday o‘zgartirayotgani va uning prostata hujayralarining ko‘payishi, apoptosi hamda androgen retseptor signalizatsiyasiga ta’siri molekulyar mexanizmlari o‘rganiladi. Ushbu polimorfizm rolini aniqlash prostata kasalliklarining genetik asoslarini yaxshiroq tushunishga yordam berishi mumkin, bu esa xavfni baholash, barvaqt tashxis qo‘yish va maqsadli davolash usullarini rivojlantirishda muhim ahamiyatga ega bo‘ladi.

Kalit so‘zlar: Prostata bezi xavfsiz giperplaziyasi (PBXG), prostata bezi saratoni (PBS), genetik polimorfizmlar, ESR1 geni, G2014A/Thr594Thr polimorfizmi.

Materials and methods

Study Subjects. The present study included 74 men who visited the clinic for LUTS between January 2022 and December 2023. Patients' clinical symptoms were assessed using the International Prostate Symptom Score (IPSS) and quality of life (QoL) questionnaires. The prostate volumes of patients were measured by transrectal ultrasonography, and the serum prostate-specific antigen (PSA) level of each subject was determined. Peak urine flow velocity (Qmax) and mean urine flow velocity (Qavg) were measured using a uroflowmetry system.

The blood analysis of associations of polymorphisms of the studied genes will be carried out using a case-control model (case-control, comparison of two samples). Genetic research and analysis of the obtained data will be carried out according to the GRIPS principles in order to increase transparency and the quality of risk prediction. PCR analysis will be carried out using thermal cyclers Applied Biosystems 2720 (USA) and CG1-96 (Corbett Research QUAGEN Germany) and Rotor GeneQ (QUAGEN Germany) in accordance with the amplification programs. When collecting blood from patients, standard vacuum tubes Vacutainer Becton Dickinson International (USA) with EDTA will be used.

Subjects were excluded from the study if they had prostate cancer, neurogenic bladder, urethral stricture, acute/chronic prostatitis, urinary tract infection, uncontrolled diabetes mellitus, previous pelvic surgery, or hypertension. Subjects were assigned to either the control group (prostate volume <30 mL) or the group with BPH [prostate volume 30 mL; IPSS, >8; Qmax, <15 mL/sec] group, depending on symptoms (11,12). All subjects provided written informed consent.

Result and discussions

In the main group of patients, the A allele was detected with a frequency of 97.6% versus 99.0% ($\chi 2$=1.3; P=0.3; OR=0.4; 95%CI:0.08- 1.96) in conventionally healthy individuals. The distribution frequency of the G allele showed that this allele was slightly higher in the main group of patients compared with the comparison group (2.4% vs. 1.0%; $\chi 2$=1.3; P=0.3; OR=2.5; 95%CI:0.51-12.4).

Table 1

Carriage of alleles and genotypes of G2014A/Thr594Thr polymorphism in ESR1 gene in the main group of patients and in the control group.

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	Main group		Control group					
	n	%	n	%				
A	207	97.6	208	99.0	1.3	0.3	0.4	0.08 – 1.96
G	5	2.4	2	1.0			2.5	0.51 – 12.4
A/A	101	95.3	103	98.1			0.4	0.08 – 1.96
A/G	5	4.7	2	1.9			2.5	0.51 – 12.74

However, no significant differences were found in the frequency distribution of A/A genotype in the compared groups (95.3% vs. 98.1%; $\chi2$=1.3; P=0.3; OR=0.4; 95%CI:0.08-1.96).

It should be noted that when carrying heterozygous A/G genotype, no significant association was found in patients in the main group in relation to healthy individuals. But, in spite of this, the risk of disease development at carrying this genotype is 2.5 times higher than in individuals without this genotype (4.7% vs. 1.9%, $\chi2$=1.3; P=0.3; OR=2.5; 95%CI:0.51-12.74).

The homozygous G/G genotype was not detected in both groups (see Table 1).

It is important to note that despite the absence of a significant association between the heterozygous A/G genotype and the development of the disease in the main group compared to the control group, there is a tendency to an increased risk of BPH in carriers of this genotype. The 2.5-fold higher risk observed in carriers of the A/G genotype, although not reaching statistical significance, may indicate the potential influence of genetic predisposition on the development of this disease. The absence of a homozygous G/G genotype in both groups may indicate the rarity of this variant in the population, which requires further study to understand its role in pathogenesis in more detail.

Additional studies, including expansion of the sample and analysis of other genetic and non-genetic factors, may help to clarify the relationship between genotypes and risk of developing BPH.

The analysis of allelic and genotypic variants frequency of G2014A/Thr594Thr polymorphism in ESR1 gene allowed us to establish that 98.0% of patients with BPH had A allele of major type, whereas in the group of conditionally healthy individuals the detection of the same allele was observed in 98.1% of cases. It should be noted that in this case there were no significant differences between the groups ($\chi2$=0.7, p=0.4, 95%CI:0.08-2.7, OR=0.5).

In addition, in contrast to the major allele A in the main group of patients with BPH, there was a more than 2.2-fold increase in the minor allele G of this polymorphic marker compared to the control group (2.0 vs. 1.0% at $\chi2$=0.7, p=0.4, 95%CI:0.37-12.51, OR=2.2).

When comparing the frequency distribution of wild-type genotype A/A of polymorphic marker G2014A/Thr594Thr in ESR1 gene in patients with BPH, there were no significant differences from healthy individuals (p>0.05), which indicates that this genotype is not associated with the risk of developing this disease (see Table 2).

Heterozygous genotype A/G of G2014A/Thr594Thr polymorphism in the ESR1 gene was detected with the highest frequency in the group of patients with BPH - 4.1% versus 1.9% of cases in the reference group. At the same time, the differences did not reach the level of threshold significance. Nevertheless, in the presence of this genotype there is a weak tendency of risk of OSA development (2.2 times) in relation to the control group ($\chi2$=0.7; P=0.4; OR=2.2; 95%CI: 0.37-12.82).

Table 2

Carriage of alleles and genotypes of G2014A/Thr594Thr polymorphism in ESR1 gene in the main group of patients with BPH and in the control group.

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	BPH		Control group					
	n	%	n	%				
A	145	98.0	208	99.0	0.7	0.4	0.5	0.08 – 2.7
G	3	2.0	2	1.0			2.2	0.37 – 12.51
A/A	71	95.9	103	98.1			0.5	0.08 – 2.71
A/G	3	4.1	2	1.9			2.2	0.37 – 12.82

However, despite the absence of statistically significant differences, the revealed trend may indicate a potential role of heterozygous genotype A/G of G2014A/Thr594Thr polymorphism in ESR1 gene in the pathogenesis of BPH. In order to confirm these findings and more accurately assess the possible influence of genotype on the risk of developing the disease, further studies with larger sample sizes and stratification by other risk factors, such as age, comorbidities and hormonal status, are needed.

As can be seen from Table 4.3, 96.9% of the examined patients with cancer were carriers of the wild-type allele A of the G2014A/Thr594Thr polymorphism of the ESR1 gene, whereas in the reference group this allele was detected in 99.9% of the participants.

There were no significant differences in the frequency of carrying the A allele between patients with AD and conventionally healthy individuals ($\chi2 = 1.6$, $p = 0.3$, 95%CI: 0.05-1.93, OR = 0.3) (see Table 3).

The frequency of the unfavorable G allele of this polymorphism was marginally higher among the RPW patients compared with controls (3.1% vs. 1.0%). Despite the non-significant difference in the frequency of the G allele, there was a moderate trend towards an increased risk of developing RPJ and the presence of this allele increased the risk of developing the above pathology 3.4-fold compared to the control group ($\chi2 = 1.6$, $p = 0.3$, 95%CI: 0.52-21.77, OR = 3.4) (see Table 3).

Thus, despite the absence of statistically significant differences in the frequency of carrying the A allele of the G2014A/Thr594Thr polymorphism of the ESR1 gene between patients with CRC and conventionally healthy individuals, there is a tendency for more frequent detection of the minor G allele among CRC patients. This may indicate a potential role of this polymorphism in predisposition to the development of this disease.

Additional studies with larger patient samples are needed to determine more precisely the contribution of genetic markers to the development of prostate cancer.

The analysis of genotyping results and statistical data processing confirms that the G2014A/Thr594Thr polymorphism may have a moderate effect on the risk of developing cancer. These findings open prospects for further investigation of the role of polymorphism in personalized medicine, where the genetic characteristics of the patient can be taken into account in the development of preventive and therapeutic strategies.

The frequency of wild-type A/A genotype was 93.8% in the studied group of patients with RPW, while in the control group this figure reached 98.1%. The differences were not statistically significant ($\chi^2=1.6$, $p=0.3$, 95%CI:0.04-1.93, OR=0.3) (see Table 3).

According to Table 4.3, there was a difference in the frequency of heterozygous genotype A/G genotype of the ESR1 genetic marker in patients with AD, with odds ratio (OR) 3.4 at $\chi^2=1.6$ and $p=0.3$ compared to controls (6.3% vs. 1.9%). This indicates that the presence of this genotype is associated with a 3.4-fold increased risk of developing RR1 compared to the reference group.

Although the results did not reach statistical significance, the presence of heterozygous A/G genotype may indicate a potential predisposition to RPV, which warrants further investigation.

Table 3.

Carriage of alleles and genotypes of the G2014A/Thr594Thr polymorphism in the ESR1 gene in the main group of patients with cancer and in the control group.

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	CP		Control group					
	n	%	n	%				
A	62	96.9	208	99.0	1.6	0.3	0.3	0.05 – 1.93
G	2	3.1	2	1.0			3.4	0.52 – 21.77
A/A	30	93.8	103	98.1			0.3	0.04 – 1.93
A/G	2	6.3	2	1.9			3.4	0.52 – 22.76

Molecular genetic studies have shown that the wild-type A allele is detected slightly more frequently (98.0%) in patients with DGPJ than in patients with RPJ, where its frequency is 96.9%. At the same time, the mutant G allele is found in 2.0% of cases in patients with DGPJ, compared to 3.1% in patients with RPJ. These differences are statistically insignificant (χ^2=0.2; p=0.7; OR=1.6; 95%CI: 0.26-9.43 for allele A and χ^2=0.2; p=0.7; OR=0.6; 95%CI: 0.11-3.88 for allele G) (see Table 4).

Table 4

Carriage of alleles and genotypes of the G2014A/Thr594Thr polymorphism in the ESR1 gene in the main group of patients with BPH and CP.

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	OR	95%CI
	BPH		CP					
	n	%	n	%				
A	145	98.0	62	96.9	0.2	0.7	1.6	0.26 – 9.43
G	3	2.0	2	3.1			0.6	0.11 – 3.88
A/A	71	95.9	30	93.8			1.6	0.25 – 9.79
A/G	3	4.1	2	6.3			0.6	0.1 – 3.93

In the course of the study it was revealed that a statistically insignificant increase in the frequency of distribution of wild-type genotype A/A of polymorphic marker G2014A/Thr594Thr in ESR1 gene was observed in patients with DPPJ compared to patients with AD - 95.9% vs. 93.8%. At the same time, there was a slight decrease in the frequency of heterozygous A/G genotype - 4.1% in patients with DPPJ compared to 6.3% in patients with RPJ. These differences did not reach statistical significance (χ^2=0.2; p=0.7; OR=1.6; 95%CI:0.25-9.79 for the A/A genotype and χ^2=0.2; p=0.7;

OR=0.6; 95%CI:0.1-3.93 for the A/G allele) (see Table 4.4), indicating that there were no convincing genetic differences in the frequencies of these genotypes between the two groups of patients.

Conclusion

Nevertheless, such data emphasize the need for further studies to better understand the potential role of genetic markers in the development of BPH and PCa. Larger studies involving more patients could provide more definitive data on possible associations between polymorphisms in the ESR1 gene and susceptibility to prostate disease.

Further study of polymorphic markers and their influence on the functional activity of genes may open new opportunities for personalized medicine, which will allow to develop more accurate methods of diagnosis and therapy for patients with prostate diseases.

LIST OF REFERENCES:

1. Alcaraz A., Carballido-Rodrigues J. Quality of Life in patients with lower urinary tract symptoms associated with BPH: change over time in real-life practice according to treatment-the Qualiprost study // Int Urol Nephrol. 2016. May:48(5):645-56. https://www.ncbi.nlm.nih.gov/pubmed/26810324
2. Joniau S., Briganti A., Gontero P. et al. Stratification of high-risk prostate cancer into prognostic categories: a European multi-institutional study // Eur Urol. 2015; 67(1):157-164.
3. Kim E.H. J.A. Brockman, Andriole G.L. The use of 5-alpha reductase inhibitors in the treatment of benign prostatic hyperplasia // Asian J. Urol. 2018;5(1):28-32.
4. Lim K.B. Epidemiology of clinical benign prostatic hyperplasia // Asian J Urol. 2017. Jul.4(3):148-151. https://www.ncbi.nlm.nih.gov/pubmed/29264223
5. Rawla P. Epidemiology of Prostate Cancer/ P.Rawla // World J Oncol. 2019;10(2):63-89.
6. Shih H.J., Huang C.J., Lin J.A. et al. Hyperlipidemia is associated with an increased risk of clinical benign prostatic hyperplasia // Prostate. 2018;78(2):113-120.
7. Sissung T.M., Price D.K., Del Re M. et al. (2014): Genetic variation: effect on prostate cancer // Biochim. Biophys. Acta 1846, 2014; 446-456.
8. Sivonova M. K., Jurečekova J., Tatarkova Z. et al. The role of CYP17A1 in prostate cancer development: structure, function, mechanism of action, genetic variations and its inhibition // Gen. Physiol. Biophys. 2017;36:487-499. doi: 10.4149/gpb_2017024
9. Vuichoud C., Loughlin K.R. Benign Prostatic Hyperplasia: epidemiology, economics and evaluation // Can J Urol. 2015;22(Suppl 1):1-6.
10. Wang G. et al. Genetics and biology of prostate cancer // Genes Dev. 2018;32(17-18):1105-1140.

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