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STUDY OF THE ROLE OF POLYMORPHIC VARIANTS OF THE Arg72Pro LOCUS OF THE TP53 GENE IN THE DEVELOPMENT OF CERVICAL INTRAEPITHELIAL NEOPLASIA IN THE FEMALE POPULATION OF TASHKENT

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ABSTRACT

In analyzing the distribution of genotypes of the Arg72Pro polymorphism of the TP53 gene among 226 patients with cervical intraepithelial neoplasia and 165 conditionally healthy women, the predominancy of the Pro allele and the rare mutant homozygous Pro / Pro genotype over the homozygous Arg / Arg genotype was established. An increase in the severity of CIN is associated with an increase in the frequency of the rare mutant homozygous Pro / Pro genotype: with LSIL, the frequency of the Pro / Pro genotype is 18.28% (OR = 1.422); with HSIL CIN II - 56.25% (OR = 7.938); at HSIL CIN III - 75.00% (OR = 18.522).

Since the presence of the Pro allele is also associated with the progression of the severity of CIN, it is obvious that genotypes with the presence of this allele are risk factors for the severity of CIN.

Keywords: Arg72Pro locus, TP53 gene, allele, genotype, Hardy-Weinberg's law, cervical intraepithelial neoplasia, homozygote, heterizygote, cervical cancer.

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分析226例宫颈上皮内瘤变患者和165例条件健康女性TP53基因Arg72Pro多态性的基因型分布，Pro等位基因和罕见突变纯合Pro/Pro基因型相对于纯合Arg/Arg基因型的优势为 已确立的。CIN 严重程度的增加与稀有突变纯合 Pro/Pro 基因型频率的增加有关：对于 LSIL，Pro/Pro 基因型的频率为 18.28% (OR = 1.422)； 使用 HSIL CIN II - 56.25% (OR = 7.938)； 在 HSIL CIN IIII - 75.00% (OR = 18.522)。

由于 Pro 等位基因的存在也与 CIN 严重程度的进展相关，因此显然具有该等位基因的基因型是 CIN 严重程度的危险因素。

关键词：Arg72Pro 基因座，TP53 基因，等位基因，基因型，Hardy-Weinberg 定律，宫颈上皮内瘤变，纯合子，杂合子，宫颈癌。

INTRODUCTION

Cervical intraepithelial neoplasia is one of the most important issues in modern gynecology. From a clinical and morphological point of view, dysplasia is a disorder of differentiation, maturation, aging and apoptosis of epithelial cells lining the cervix. According to the severity of dysplastic changes, morphologically, mild (CIN I), moderate (CIN II) and severe (CIN III) dysplasia are distinguished. CIN I is characterized by polymorphism of cellular elements with pronounced hyperchromicity of the nuclei and a high nuclear-cytoplasmic ratio, with the involvement of a third part of the stratified squamous epithelium. In the case of CIN II, cellular atypism and numerous mitoses are determined. CIN III is characterized by cellular atypism. According to the WHO classification (1982) and Bethesda (2001, 2004, 2014), the concepts of severe dysplasia and cancer in situ are combined into one pathological process (CIN III and HSIL) [1,7,9,13].

Despite significant advances in the treatment of oncological pathology of the cervix, its prevalence is not decreasing, but steadily increasing [2, 3]. At the stage of CIN and microinvasive cervical cancer (MICC), the disease is diagnosed extremely rarely, and the majority of patients present with a detailed clinical picture of the invasive process [10,15]. It determines the importance of identifying the risk factors for carcinogenic remodeling of the cervical epithelium, leading to an unfavorable course of the disease. These include molecular testing of genes called “predisposition” genes or candidate genes [14].

Human protein-coding genes have molecular differences (polymorphisms) in their structure, leading to the synthesis of proteins with slightly altered structural and functional characteristics. Their features determine not only a person`s predisposition to certain diseases, but also the nature of their course in the case of the development of pathology [12, 14, 17]. The study of the genetic specificity of the development of CIN is necessary for the development of prevention and treatment measures. Obviously, to assess the prognosis of the course and determine the risk of neoplastic transformation of neoplasias, knowledge of the molecular genetic characteristics of its development is necessary.

The TP53 gene encodes the p53 protein, which regulates target genes that cause cell cycle inhibition, apoptosis, aging, DNA repair or changes in metabolism, acts as a tumor suppressor in many types of tumors, stimulates apoptosis or growth retardation depending on physiological conditions and cell type,

responding to a variety of stress effects on cells. The level of expression of the p53 protein in normal cells is reduced, an increased level of expression is observed in various transformed cell lines, where the p53 protein contributes to the transformation and formation of malignant neoplasms. Mutant p53 proteins have a reduced oncosuppressive activity; somatic mutations of this gene are associated with human malignant neoplasms [3,5,6,8, 14,18].

Molecular genetic mechanisms of persistence, regression or progression of cervical intraepithelial neoplasia up to invasive cancer are not fully studied and not clear.

The aim of the research is to study the associations of allelic variants of the Arg72Pro polymorphic locus of the TP53 gene in patients with various severity of cervical intraepithelial neoplasia.

MATERIAL AND METHODS

The study included 391 women of fertile age from 18 to 45 years, of which 226 patients with cervical intraepithelial neoplasia and 165 patients without pathology of the organs of the reproductive system made up the control group.

In working with patients, the ethical principles set forth by the Declaration of Helsinki of the World Medical Association “Ethical principles of scientific and medical research with human participation” were observed.

The criteria for inclusion of women in the clinical study group were: the presence of cervical intraepithelial neoplasia, the absence of therapy with immunomodulatory drugs in the last 6 months, and exacerbation of chronic inflammatory processes in the small pelvis. The study also did not include women under 18 and over 45 years old, with a positive pregnancy test, with severe somatic pathology, as well as patients taking medications that could affect the studied parameters.

On the basis of the clinical and cytological studies, 186 patients of the main group were diagnosed with mild CIN I; the moderate CIN II was found in 32 patients, and severe (CIN I), moderate (CIN II) and severe (CIN III) were diagnosed in 8 patients. The control group (control group) consisted of 165 patients of comparable age, social and marital status, who applied to antenatal clinics for a preventive examination.

During the comprehensive examination, a colposcopic examination was performed, smears were taken for the degree of vaginal frequency, bacterial culture from the vagina, test for sexually transmitted infections using polymerase chain reaction (PCR), oncocytology from the cervix, and ultrasound examination of the pelvic organs.

Isolation of genomic DNA from whole blood was performed using the Ampli Prime Ribot-prep reagent kit (Next Bio LLC, Russia). Detection of DNA samples from the Arg72Pro locus of the TP53 gene was carried out by allele-specific PCR on an Applied Biosystems 2720 thermal cycler, using SPF Litekh kits, according to the manufacturer's instructions.

The estimation of the deviation of the frequencies of the observed and expected genotypes from the canonical Hardy-Weinberg distribution was carried out using the GenePop genetic-population program package (Rousset F. genepop'007: a complete re-implementation of the genepop software for Windows and Linux // Molecular Ecology Resources, 2008. - Vol. 8. - No. 1. - P. 103-106.).

In the sample of patients with cervical intraepithelial neoplasia and in the control group (without pathology of the reproductive organs),

the distribution of alleles and genotypes was checked for the observance of the Hardy-Weinberg equilibrium (p2AA + 2pqAa + q2aa = 1).

To assess the association between the studied parameters and the risk of developing the analyzed event, the odds ratio (OR) was calculated with a 95% confidence interval (CI). When comparing the frequencies of features, the standard Pearson $\chi 2$ test and Fisher's exact test were used.

RESULTS

The main task that solves the problem of preventing oncological pathology is the implementation of studies that determine the diagnostic value of the studied gene polymorphisms.

For this purpose, studies were carried out on a cohort of patients with clinically and cytologically verified CIN of varying severity, which will make it possible to assess both the diagnostic and prognostic value of the studied genetic markers.

At the first stage of this work, the distribution of allele and genotype frequencies of TP53 gene polymorphisms was calculated in the group of patients with cervical intraepithelial neoplasia and the control sample.

Statistical analysis of the differences in the distribution of the Arg72Pro alleles of the TP53 gene and the genotypes of the TP53 gene polymorphism between the group of patients with cervical intraepithelial neoplasia and the control group of women without pathology of the reproductive system made it possible to establish that the "cases" and "control" are in Hardy - Weinberg equilibrium, which makes it possible to analyze the data and compare the results of the study (Table 1).

Table 1

Expected and observed frequencies of genotypes of Arg72Pro polymorphism of TP53 gene according to Hardy-Weinberg distribution

The main group of the patients with CIN n = 226					
Alleles	**Allele frequency**				
Arg	0,53				df
Pro	0,47				1
Genotypes	**Genotype frequency**		χ^2	P	df
	Observed	Expected			
Arg/Arg	0,31	0,28	0,216	0,642 P>0,05	
Arg/Pro	0,44	0,50	0,723	0,396 P>0,05	
Pro/Pro	0,25	0,22	0,250	0,617 P>0,05	
Total	1,0	1,0	0,727	0,696 P>0,05	2
Control group n=165					
Alleles	**Allele frequency**				
Arg	0,62				df

Pro	0,38				1
Genotypes	**Genotype frequency**		χ^2	P	df
	Observed	Expected			
Arg/Arg	0,39	0,39	0,00	1,0 P>0,05	
Arg/Pro	0,47	0,47	0,00	1,0 P>0,05	
Pro/Pro	0,14	0,14	0,00	1,0 P>0,05	
Total	1,0	1,0	0,00	1,0 P>0,05	2

Analysis of combinations of allelic variants of polymorphism at the Arg72Pro locus of the TP53 gene showed that in patients with cervical intraepithelial neoplasia, there is a statistically significant increase in the frequency of occurrence of the Pro allele, which amounted to 47.35%, versus 37.58% in practically healthy women (control group) (χ^2 = 7.418; P≤ 0.007; OR = 1.495; DI 95% 1.118 - 1.995). A decrease in the frequency of carriage of the Arg allele was found to be 52.65% versus 62.42%, respectively (χ^2 = 7.418; P≤ 0.007; OR = 0.669; DI 95% 0.501 - 0.894). A decrease in the carriage of the Arg allele has a protective effect on CIN occurrence risks.

Analysis of the distribution of often genotypes showed a statistically significant difference between the groups in the frequency of registration of the homozygous Pro / Pro genotype: in patients with cervical intraepithelial neoplasia, the carrier frequency was 25.66% versus 13.94% in the control group (χ^2 = 7.982; P≤ 0.005; OR = 2.131; DI 95% 1.252 - 3.629).

Table 2

Comparative analysis of the frequency distribution of alleles and genotypes of the Arg 72 Pro polymorphism of the TP53 gene in patients with cervical intraepithelial neoplasia

Genotypes and alleles of Arg72Pro polymorphism of TP53 gene	Characteristics of the examined patients		χ^2; P	OR; 95% CI
	Main group with CIN n = 226	Control group n = 165		
Genotypes				
Arg/Arg	70/30,97	64/38,79	2,585; P>0,108	0,708 0,465-1,079
Arg/Pro	98/43,36	78/47,27	0,589; P>0,443	0,854 0,571-1,278
Pro/Pro	58/25,66	23/13,94	7,982; P<0,005	2,131 1,252-3,629
Σ	226/100,0	165/100,0		

Alleles				
Arg	238/52,65	206/62,42	7,418 P<0,007	0,669 0,501-0,894
Pro	214/47,35	124/37,58		1,494 1,118-1,995
Σ	452/100,0	330/100,0		

There was a statistically insignificant decrease in the frequency of carriage of the heterozygous genotype Arg / Pro, which amounted to 43.36% in patients with CIN versus 47.27% in the control group ($\chi^2 = 0.589$; $P \geq 0.05$; OR = 0.854; DI 95% - 0.571 - 1.278) and an insignificant decrease in the frequency of carriage of the homozygous genotype Arg / Arg, respectively, 30.97% versus 48.79% ($\chi^2 = 2.585$; $P \geq 0.05$; OR = 0.708; DI 95% 0.465 - 1.079) (Table 2).

Thus, the homozygous Arg / Arg state of the analyzed polymorphic variant is more favorable for carriers than the rare homozygous Pro / Pro variant. The discovered protective nature of Arg / Arg can be explained by its association with a low level of TP53 gene transcription. Since the carriage of the Pro allele is also associated with CIN, genotypes with this allele's presence are risk factors for the severity of CIN.

Our results on the nature of the distribution of allelic and genotypic variants of the Arg72Pro polymorphism of the TP53 gene in patients with cervical intraepithelial neoplasia are similar to the patterns obtained in other population studies in Europe. According to the authors, the Pro / Pro mutant genotype's presence leads to more pronounced inflammatory clinical symptoms, and the homozygous Arg / Arg genotype has a more favorable variant. The Pro / Pro genotype has been shown to be associated with breast cancer.

Despite the intensive study of the influence of the polymorphism of the Arg72Pro locus of the TP53 gene on the progression of pathology of the cervix uteri and organs of the reproductive system, the data on the formation of the severity of the pathology and its oncological transformation are contradictory.

It is currently considered an indisputable fact that combinations of genetic characteristics (intergenic interactions) differ significantly in different populations [12, 14]. Obviously, the effect of PT53 polymorphism is determined by many factors, the leading of which is the degree of differentiation, maturation, aging, and apoptosis of epithelial cells lining the cervix, which determines the relevance of further studies to expand the understanding of the role of TP53 genetic polymorphism in the progression and oncological transformation of cervical intraepithelial neoplasia.

In this connection, we analyzed the distribution of alleles and genotypes of the Arg72Pro polymorphism of the TP53 gene in patients with cervical intraepithelital neoplasia in the dynamics of increasing the severity of the pathology (Tables 3 - 4).

Table 3

Allele frequency distribution of Arg 72 Pro polymorphism of TP53 gene in patients with different severity of cervical intraepithelial neoplasia

Diagnosis	Alleles	**Allele Arg**	**Allele Pro**

CIN		Frequency	χ^2 P	OR 95% CI	Frequency	χ^2 P	OR 95% CI
LSIL n=186	372/100,0	204/54,84	4,142 P<0,042	0,725 0,536-0,981	168/45,16	4,142 P<0,042	1,379 1,019-1,867
HSIL CIN II n=32	64/100,0	28/43,75	7,751 P<0,006	0,464 0,270-0,799	36/56,25	7,751 P<0,006	2,153 1,252-3,703
HSIL CIN III n=8	16/100,0	6/37,50	3,995 P<0,046	0,535 0,127-0,010	10/62,5	3,995 P<0,046	2,791 0,990-7,870
Σ	452/100,0	238/52,65	7,418 P<0,007	0,689 0,501-0,894	214/47,35	7,418 P<0,007	1,494 1,118-1,995
Control group n=165	330/100,0	206/62,40			124/37,5		

A statistically significant increase in the growth in the Pro allele frequency, synchronized with the severity of the disease, was established.

With a relatively favorable course in patients with clinically and colposcopically verified LSIL, the frequency of carriage of the Pro allele was 45.16%. It was lower than the prevalence in the control group - 54.84% ($\chi^2 = 4.142$; $P \leq 0.042$; OR = 0.725; CI 95 % 0.536 - 0.981); then, with an increase in the severity of the clinical course of HSIL CIN II, the frequency of the Pro allele increased to 56.25% versus 43.75% ($\chi^2 = 7.751$; $P \leq 0.006$; OR = 2.153; CI 95% 1.252 - 3.703); and in patients with a high risk of malignant transformation with HSIL CIN III, the frequency of the Pro allele increased to 62.50% versus 37.50% ($\chi^2 = 3.995$; $P \leq 0.046$; OR = 2.791; CI 95% 0.990 - 7.870). Thus, carriage of the Pro allele increased the risk of CIN II by 2.153 times, and the risk of CIN III by 2.791 times; whereas the carriage of the Arg allele, on the contrary, reduced these risks by 0.464 and 0.535 times (Table 3).

Analysis of the frequency distribution of the genotypes of the Arg72Pro polymorphism of the TP53 gene revealed a statistically significant increase in the frequency of the Pro / Pro genotype, adapted to the severity of CIN (Table 4).

Thus, the frequency of carriage of the homozygous Pro / Pro genotype progressively increased in the series CIN I → CIN II → CIN III from 22.50%; up to 37.50% and 50.00% versus 13.94% in the control group, significantly exceeding the indicators of the control group in patients with CIN I ($\chi^2 = 4.327$; $P \leq 0.038$; OR = 1.801; CI 95% 1.030 - 3.194); CIN II ($\chi^2 = 10.183$; $P \leq 0.002$; OR = 3.368; CI 95% 1.468 - 7.723) and CIN III ($\chi^2 = 7.533$; $P \leq 0.002$; OR = 6.174; CI 95% - 1.442 - 26.433). Thus, the carriage of the homozygous Pro / Pro genotype increases the risk of the disease in patients with CIN I by 1.801 times; with CIN II - 3.368 times and with CIN III - 6.174 times.

There was a statistically insignificant decrease in the frequency of carriage of the heterozygous genotype Arg / Pro, equal to 45.70% for CIN; with CIN II - 31.25% and with CIN III 37.50% versus 47.27% in the control group. The frequency of the homozygous Arg / Arg genotype in patients with CIN was lower than the frequency of carriage in the control group. However, this difference did not have statistically significant differences. Thus, in

patients with CIN I, the frequency of carriage of the homozygous genotype Arg / Arg is 31.72% (χ^2 = 1.919; P≥0.167; OR = 0733; CI 95% 0.472 - 1.138); with CIN II - 31.25% (χ^2 = 0.649; P≥0.421; OR = 0717; CI 95% 0.319 - 1.613) and CIN III 12.50% (χ^2 = 2.248; P≥0.134; OR = 0225; CI 95 % 0.027 - 1.876) versus carriage frequency 38.90% in the control group. Thus, the carriage of the homozygous genotype Arg / Arg has a protective effect on the risk of developing cervical neoplasia, reducing the squeak of the development of the disease by 0.733, 0.717, and 0.225 times, respectively (Table 4).

A reliable association of the homozygous Pro / Pro genotype of the Arg72Pro locus polymorphism of the TP53 gene with CIN and a statistically significant increase in the frequency of carriage of this genotype with an increase in the severity of pathology may be evidence of the pathogenetic significance in complex molecular genetic changes that determine the severity of the clinical course of CIN.

Table 4

Comparative analysis of the frequency distribution of the genotypes of the Arg 72 Pro polymorphism of the TP53 gene in patients with varying severity of cervical intraepithelial neoplasia

CIN diagnosis	Genotype Arg/A			Genotype Arg/Pro			Genotype Pro/Pro		
	Frequenc	χ^2 P	OI 95% CI	Frequen	χ^2 P	OI 95% CI	Frequen	χ^2 P	C 95% CI
LSIL n=186/100	59/31,72	1,919 P>0,16	0,73 0,472-1,138	85/45,70	0,087 P>0,76	0,939 0,617-1,429	42/22,58	4,327 P<0,03	1,80 0,030-3,149
HSIL CIN n=32/100,	10/31,25	0,649 P>0,42	0,71 0,319-1,613	10/31,25	2,784 P>0,09	0,501 0,226-1,137	12/37,50	10,183 P<0,00	3,36 1,468-7,723
HSIL CIN I n=8/100,0	1/12,5	2,248 P>0,13	0,22 0,027-1,876	3/37,5	0,293 P>0,58	0,669 0,155-2,892	4/50,0	7,533 P<0,00	6,17 1,442-26,433
Σ-226/100,	70/30,97	2,585 P>0,10	0,70 0,465-1,079	98/43,36	0,589 P>0,44	0,854 0,571-1,278	58/25,66	7,982 P<0,00	2,13 1,252-3,629
Control group n=165	64/38,79			78/47,27			23/13,94		

DISCUSSION

It is difficult to predict the biological behavior of cervical cells at the precancerous stage and in the early stages of oncological transformation. In this regard, the identification of new markers that make it possible to accurately predict the evolution of the disease is of great importance. In addition, it is difficult to determine the stage of

the disease, differential diagnosis of benign and malignant disorders [13, 15, 16]. It is noted that 94 cases of cervical cancer identified types of human papillomavirus [1, 7, 9].

In the pathogenesis of the atypical process in the cervix, the leading role is assigned to the human papillomavirus (HPV). During replication of the virus, its DNA penetrates into the genome of the infected cell, stimulating proliferative processes in it and suppressing apoptosis of cells of the cervical epithelium [2, 4, 9, 11, 18].

Analysis of modern literature shows that a large amount of research is currently being carried out on the development of objective molecular genetic criteria for predicting the course of cervical diseases [1,4,8,12,15]. That dictates the need to analyze changes in genes of proliferation, apoptosis and differentiation in cervical intraepithelial neoplasia in cervical cancer [6,14].

Of particular interest is the involvement of TP53 gene abnormalities in the development of different types of tumors, which is explained by the performance of a wide range of functions that prevent and / or inhibit tumor growth [5,6, 9, 15].

When analyzing the distribution of the genotypes of the Arg72Pro polymorphism of the TP53 gene among 226 patients with cervical intraepithelial neoplasia and 165 apparently healthy women, the prevalence of the rare mutant homozygous Pro / Pro genotype over the homozygous Arg / Arg genotype was established.

Polymorphic loci of the TP53 gene are actively studied by many researchers in oncological pathologies of various localization. In oncological pathology, the high diagnostic and prognostic significance of polymorphic loci of the TP53 gene has been shown. Single-nucleotide polymorphism of Arg72Pro 4 exon of TP53 gene is characterized by substitution in 72 codons of base G by base C. It leads to amino acid substitution in the primary structure of the corresponding protein arginine for proline. This polymorphism is associated with the risk of developing oncological and somatic pathologies of various origins [3, 5]. The unfavorable Pro / Pro genotype enhances the expression of the mutant p53 protein, which has pro-oncogenic properties [2, 6].

In our studies, the progression of CIN severity is associated with an increase in the frequency of the rare mutant homozygous Pro / Pro genotype: in LSIL, the frequency of the Pro / Pro genotype is 18.28% (OR = 1.422); with HSIL CIN II - 56.25% (OR = 7.938); at HSIL CIN III - 75.00% (OR = 18.522).

Since the presence of the Pro allele is also associated with the progression of the severity of CIN, it is obvious that genotypes with the presence of this allele are risk factors for the severity of CIN.

CONCLUSION

To sum up, our study showed that the development of CIN is associated with the carriage of the Pro allele and the rare mutant homozygous Pro / Pro genotype. The presence of Pro / Pro genotype of the Pro polymorphism of the Arg72Pro locus of TP53 gene in women can be considered as a high risk of developing cervical intraepithelial neoplasia.

According to the analysis, it was found that the formation of CIN reveals significant changes in polymorphic variants of the Pro / Pro genotype of the Arg72Pro TP53 locus gene. Disruption of programmed cell death as a result of TP53 dysfunction may be a trigger factor for the development of neoplastic changes in the

cervical epithelium and progression to cervical cancer.

CONFLICT OF INTERESTS AND CONTRIBUTION OF AUTHORS

The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article and report on the contribution of each author.

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