

Analysis of the role of 1G / 2G polymorphism in the MMP1 gene in the development and clinical course of cervical intraepithelial neoplasia

I.A. Kamilova, J.E. Pakhomova, D.K. Nadjmutdinova
Tashkent Medical Academy Republic of Uzbekistan

Abstract: *In the present work, the frequency of occurrence of polymorphic variants 1607 1G / 2G (rs 1799750) of the MMP1 gene encoding enzymes of collagen metabolism and its genotypes in patients with cervical intraepithelial neoplasia and healthy women in Tashkent was first investigated. A statistically significant association of 2G allele carriage with a risk of developing CIN ($\chi^2 = 15.4$; $P \leq 0.001$) and unreliable with carriage of the heterozygous genotype 1G / 2G ($\chi^2 = 1.36$; $P \geq 0.243$) were established. In the control group of patients, a statistically significant predominance of the 1G allele ($\chi^2 = 29.4$; $P \leq 0.001$) and the homozygous genotype 1G / 1G ($\chi^2 = 19.6$; $P \leq 0.001$) was found. The highest values of the carriage of the 2G allele and homozygous genotype 2G / 2G were found at CIN and at CIN III. Thus, the study of polymorphism rs 1799750 of the MMP1 gene is promising for predicting the course of cervical intraepithelial neoplasia and can be used to form risk groups for the development of this pathology.*

The frequency distribution of alleles and genotypes of the polymorphic marker rs1799750 of the MMP1 gene in patients with CIN did not correspond to the canonical Hardy-Weinberg distribution due to an increase in the frequencies of homozygous genotypes and a decrease in the frequency of the heterozygous genotype; in the control group, the frequency distribution of alleles and genotypes of the polymorphic marker rs 1799750 of the MMP1 gene corresponded to the canonical Hardy-Weinberg distribution.

Keywords: *MMP1 gene, polymorphism, allele, genotype, Hardy-Weinberg, cervical intraepithelial neoplasia.*

Cervical intraepithelial neoplasia (CIN) is a chronic continuously progressive disease of the cervix, the main characteristic of which is the neoplastic transformation of cervical epithelium of the tissues of the cervix with subsequent pathological multiplication of cells with signs of atypia. The prolonged existence of neoplasia can become the basis of oncological transformation of the cervix. It should be noted that CIN lacks clearly defined clinical symptoms, and the basis of diagnosis is the data of cytological and histological studies [1,2].

The pathological process is directly related to the activity of the human papilloma virus. Nevertheless, the presence of a highly oncogenic type of virus is not a sufficient prognostic marker, in view of the high probability of spontaneous elimination of the virus. The lesions characteristic of CIN 1 can also be caused by infectious and inflammatory processes caused by various urogenital infections, and by dystrophic processes in the cervix, and conditions associated with estrogen deficiency [1,2,8,10].

The high prevalence of CIN, the polymorphism of occurrence, the risk of precancerous changes and cervical cancer - all this determines the urgency of the problem of

early diagnosis and prognosis of oncological transformation of uterine epithelial neoplasia [1,10].

The disease is a chronic neoplastic process in which there are morphological changes in the structure of the epithelium, damage to the thickness of the epithelial layer and the basement membrane [9]. The development of a neoplastic transformation of cervical epithelium is associated with inflammation involving cytokines and other inflammatory mediators. Long-term persistence of inflammation leads to damage to the thickness of the epithelial layer and basement membrane, dystrophic changes in the intercellular matrix, pathological angiogenesis, etc. Participation in the inflammatory process of macrophages, neutrophils, cytokines and other inflammatory mediators leads to the degradation of the extracellular matrix [2, 10].

Maintaining the normal state of the extracellular matrix (type I and IV collagen) between the cervical epithelium and the basement membrane is regulated by matrix metalloproteinases (MMPs) [4,7,19]. The synthesis and secretion of metalloproteinases is carried out not only by a number of normal cells: neutrophils, monocytes, macrophages, fibroblasts, osteoclasts, chondrocytes, keratinocytes, endothelial and epithelial cells, but also by oncogene-transformed cells [4,11,20].

Collagenases are the first, most studied class of metalloproteinases. Currently, four representatives of this family are known: interstitial collagenase, or type I collagenase (MMP-1), neutrophil collagenase (MMP-8), collagenase 3 (MMP-13), collagenase 4 (MMP-18). MMP-1 is the first tissue enzyme that hydrolyzes the helical region of collagen [21,22]. The main collagenase substrate is spiral fibrillar collagen of types I, II, and III, the degradation products of which become a substrate for further cleavage by gelatinases and stromelysins. Interstitial collagenase (MMP-1) is synthesized by a number of cells: normal and transformed fibroblasts, chondrocytes, epithelial cells, including keratinocytes, macrophages, osteoblasts, and is active against type III collagen [25].

Impaired collagen metabolism of connective tissue may be associated with a mutation of genes that regulate collagen synthesis and the formation of extracellular matrix [4,24,26].

For MMP genes, as well as for many other genes, polymorphism is characteristic - the presence in the population of alleles with one or another nucleotide sequence. Polymorphic genetic loci may not cause any changes in the phenotype, but may have a functional effect, affecting the level of gene expression and the amount of protein product, or on the stability and functional characteristics of the protein as an enzyme [18, 20].

Compelling evidence has been obtained of the role of methylation of MMP genes in the formation of cancer of the reproductive system [15,17,21]. But, despite this, the question remains open about their place in the chain of the pathogenesis of CIN. The study of the methylation status of genes encoding matrix metalloproteinase proteins at various stages of the development of CIN is necessary to establish the role of these genes in the oncological transformation of neoplastic processes of the cervical canal.

The aim of the study was to evaluate the importance of polymorphism rs 1799750 of the MMP-1 gene in the formation of cervical epithelial dysplasia and the development of cervical intraepithelial neoplasia.

Material and methods

A complete clinical and laboratory examination of 226 women aged 18 to 45 years (average age 47.82 ± 6.6 years) who were diagnosed with cervical intraepithelial neoplasia was performed, the control group consisted of 165 women of comparable age and social status, which increased the reliability of the control. During the gynecological examination, a gynecological anamnesis of patients of both groups was collected, the cervix was examined, a cytological examination, simple and extended colposcopy, and bimanual vaginal examination were performed.

The presence or absence of cervical neoplasia of the cervix in women was established on the basis of the analysis of anamnestic and clinical data, the results of a gynecological examination and cytological examination.

When studying the data of cytological studies, they were guided by the international classification of cervical pathology Beta.

Analysis of the data of gynecological examination and cytological examination showed that 186 patients of the main group were diagnosed with mild CIN I, moderate CIN II was detected in 32 patients and severe (CIN III) III was registered in 8 patients.

The control group was formed from 165 unrelated healthy Uzbek women.

Genomic DNA was isolated from whole blood using the "AmpliPrime RIBO-Prep" reagent kit (Next Bio LLC, Russia). Detection of DNA samples by rs1799750 of the MMP-1 gene was carried out by allele-specific PCR on an Applied Biosystems 2720 thermal cycler, using Litekh NPF kits, according to the manufacturer's instructions.

The deviation of the frequencies of the observed and expected genotypes from the Hardy-Weinberg canonical distribution was estimated using the "GenePop" 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.).

Statistical processing of the results obtained data was performed using the OpenEpi statistical software package (version 9.2). The criterion that determines whether the trait under investigation is a risk factor for the disease was the odds ratio (OR). Significance of differences was evaluated by the Pearson χ^2 criterion.

Results

Early diagnosis of CIN remains the main unsolved problem of modern oncogynecology. Identification of hereditary forms of this disease associated with rs 1299750 mutations in the MMP-1 gene allows women with a high risk of CIN to be distinguished and makes screening programs promising [7,12, 15].

One of the most important pathogenetic mechanisms determining dystrophic changes in the intercellular matrix, inflammation and pathological angiogenesis, the progression of neoplasia and its oncological transformation are the destruction of the extracellular matrix (type I and IV collagen) between the cervical epithelium and the basement membrane [4]. What determined the relevance of the study of the relationship of the genetic polymorphism of the enzyme involved in collagen metabolism with the risk and severity of the clinical course of CIN.

In studies, it was found that in patients with CIN, the frequency of the 2G allele statistically significantly prevails compared with the control. Thus, the frequency of the 2G allele in the total sample of patients with CIN was 48.67%, while in the control it was 29.39% ($\chi^2 = 29.410$; $P \leq 0.001$; OR = 2.278; 95% DI - 1.687 - 3.075). Thus, the presence of the 2G allele increases the risk of CIN by more than 2.278 times. In this case, the carriage of the 1G allele, on the contrary, has a protective effect, reducing the risk of CIN (OR = 0.439): in patients with CIN, the frequency of carriage of the 1G allele was 48.67%; in the control, 29.39% ($\chi^2 = 29.4$; $P \leq 0.001$; OR = 0.4; 95% DI - 0.325 - 0.593) (Table 1).

Table 1
Comparative analysis of the frequency distribution of alleles and genotypes of 1G / 2G polymorphism in the MMP-1 gene (MMP-1 according to 1607 1G / 2G rs 1799750) in patients with cervical intraepithelial neoplasia and in the control group

Genotypes and alleles polymorphism 2G of the MMT-1 gene (MMT-1 coding to 1607 1G / 2G rs 1799750)	Characteristic		x ² P	OR 95% CI
	Patients with CIN n=226	Control group n=165		
Genotypes				
1G/1G	69/30,5	87/52,7	19,595 P<0,001	0,394 0,260-0,598
1G/2G	94/41,6	59/35,8	1,4 P>0,243	1,3 0,847-1,935
2G/2G	63/27,9	19/11,5	15,4 P<0,001	2,97 1,697-5,197
Σ	226/100,0	165/100,0		
Alleles				
1G	232/51,3	233/70,6	29,4 P<0,001	0,4 0,325-0,593
2G	220/48,7	97/29,4		2,278 1,687-3,075
Σ	452/100,0	330/100,0		

Analysis of the distribution of genotype frequencies for 1607 1G / 2G rs 1299750 revealed a statistically insignificant increase in the detection frequency of the 1G / 2G heterozygous genotype in patients with cervical intraepithelial neoplasia 41.59% versus 35.765% in the control group ($\chi^2 = 1.4$; $P \geq 0.243$; OR = 1.3; CI 95% 0.847 - 1.935) and a significant increase in the carrier frequency of the "mutant" homozygous 2G / 2G genotype to 27.88% versus 11.51% in the control group ($\chi^2 = 15.4$; $P \leq 0.001$; OR = 2.97; CI 95% 1,697 - 5,197). Moreover, the carrier frequency of the "normal" homozygous 1G / 1G genotype was statistically significantly reduced 30.53% versus 52.73% ($\chi^2 = 19.6$; $P \leq 0.001$; OR = 0.4; CI 95% 0.260 - 0.598) (Table 2).

A significant effect of changes in the frequency of carriage of alleles and heterozygous and mutant homozygous genotypes on the severity of cervical neoplasia has been established (Tables 2 - 3).

Table 2: Comparative analysis of the frequency distribution of alleles of the polymorphic marker 1G / 2G of the MMT-1 gene in patients with varying severity of cervical intraepithelial neoplasia

CIN diagnosis	Alleles	Allele 1G			Allele 2G	
		Frequency	χ^2 P	OR 95% CI	Frequency	χ^2 P
LSIL n=186	372/100,0	202/54,30	20,752 P<0,001	0,911 0,676-1,228	170/45,70	19,7 P<0,001
HSIL CIN II n=32	64/100,0	24/37,5	26,675 P<0,001	0,250 0,143-0,437	40/62,5	25,903 P<0,001
HSIL CIN III n=8	16/100,0	6/37,5	8,091 P<0,005	0,250 0,088-0,706	10/62,50	7,8 P<0,006
Σ	452/100,0	232/51,33	29,440 P<0,001	0,439 0,325-0,593	220/48,67	29,410 P<0,001
Control group n=165	330/100,0	233/70,61			97/29,39	

In order to study the characteristics of matrix metalloproteinase genes in the implementation of the inflammatory response of the intercellular matrix at various stages of cervical neoplasia, their activity was evaluated in patients with various severity of CIN.

It should be noted that the frequency of carriage of the “wild” 2G allele increases simultaneously with the severity of the clinical course of CIN: in patients with a relatively favorable course (LSIL), the frequency of the 2G allele was 45.7%, which is statistically significantly higher than the control indicator - 29.4% ($\chi^2 = 19.7$; $P \leq 0.001$; OR = 2.0; CI 95% 1.479 - 2.763); in more severe cases in patients with HSIL, CIN II and CIN III, the 2G allele frequency increased to 62.50% ($\chi^2 = 25.9$; $P \leq 0.001$; OR = 4.0; CI 95% 2.290 - 7.00) and ($\chi^2 = 7.8$; $P \leq 0.006$; OR = 4.0; CI 95% 1.416 - 11.321). Moreover, the carriage of the “normal” 1G allele is associated with a protective effect on the severity of the pathology: its carriage frequency decreases from 54.30% with LSIL to 37.50% with HSIL CIN II and CIN III against 70.61% in the control (Table 2).

Analysis of the genetic polymorphism of the genotypes of the 1G / 2G polymorphic marker in the MMT-1 gene in patients with different severity of the clinical course showed the high importance of carriage of the “mutant” 2G / 2G homozygous genotype at the risk of increased CIN severity (Table 3). So, with LSIL, the frequency of the 2G / 2G genotype of the 2G allele was 25.3%, which is statistically significantly higher than the control indicator - 11.5% ($\chi^2 = 10.8$; $P \leq 0.001$; OR = 2.6; CI 95% 1.453 - 4.646); with a more severe course in patients with HSIL CIN II, the 2G allele frequency increased to 37.5% ($\chi^2 = 13.6$; $P \leq 0.001$; OR = 4.6; CI 95% 1.950 - 10.920); and in patients with a risk of malignant malignancy with HSIL CIN III, the 2G allele frequency increased to 50.0% ($\chi^2 = 9.8$; $P \leq 0.002$; OR = 7.7; CI 95% 1.774 - 33.289) (Table 3).

In patients with CIN, a statistically insignificant increase in the carrier frequency of the heterozygous genotype 1G / 2G was found: with LSIL - 41.4% versus 35.8% in the control ($\chi^2 = 1.2$; $P \geq 0.279$; OR = 1.34; CI 95% 0.840 - 1.990); with HSIL CIN II - 43.7% ($\chi^2 = 0.7$; $P \geq 0.392$; OR = 1.4; CI 95% 0.661 - 3.066) and with CIN III - 37.5% ($\chi^2 = 0.01$; $P \geq 0.921$; OR = 1.1; CI 95% 0.254 - 4.758) (Table 3).

The frequency of carriage of the “normal” homozygous genotype 1G / 1G decreases with increasing severity of neoplastic processes of the cervical epithelium, which indicates its protective role in reducing the severity of pathologies and reducing the severity of neoplastic processes of cervical epithelium. With LSIL, the carrier frequency of the “normal” 1G / 1G genotype was 33.33% versus 52.7% in the control ($\chi^2 = 13.5$; $P \leq 0.001$; OR = 0.3; CI 95% 0.222 - 0.517); with HSIL CIN II - 18.7% ($\chi^2 = 12.4$; $P \leq 0.001$; OR = 0.2; CI 95% 0.081 -

0.529) and with CIN III - 12.5% ($\chi^2 = 4.9$; $P \leq 0.027$; OR = 0.1; CI 95% 0.015 - 1.064) (Table 3).

The "wild" 1G allele inhibits the synthesis of MMR1, which leads to a decrease in the hydrolysis of collagen and proteins of the connective tissue matrix and is associated with a decrease in the severity of CIN. Carrying the "mutant" 2G allele, in contrast, is associated with the risk of CIN and increases with increasing severity of disease. Genotypes with the 2G allele have also been found to be risk factors for disease development.

Table 3
Comparative analysis of the frequency distribution of genotypes of the polymorphic marker 1G / 2G of the MMT-1 gene in patients with varying severity of cervical intraepithelial neoplasia

CIN diagnosis	Genotype 1G/1G			Genotype 1G/2G			Genotype 2G/2G		
	Frequency	χ^2 P	OR 95% CI	Частота	χ^2 P	OR 95% CI	Frequency	χ^2 P	OR 95% CI
LSIL n=186	62/33,3	13,5 P<0,001	0,3 0,222-0,517	77/41,4	1,2 P>0,279	1,3 0,840-1,990	47/25,27	10,8 P<0,001	2,6 1,453-4,646
HSIL CIN II n=32	6/18,7	12,4 P<0,001	0,2 0,081-0,529	14/43,7	0,7 P>0,392	1,4 0,661-3,066	12/37,5	13,6 P<0,001	4,6 1,950-10,920
ISIL CIN III n=8	1/12,5	4,9 P<0,027	0,1 0,015-1,064	3/37,5	0,01 P>0,921	1,1 0,254-4,758	4/50,0	9,8 P<0,002	7,7 1,774-33,289
Σ -226	69/30,53	19,595 P<0,00	0,34 0,260-0,598	94/41,59	1,363 P>0,243	1,279 0,847-1,935	63/27,88	15,403 P<0,00	2,970 1,697-5,197
Control group n=165	87/52,7			59/35,8			19/11,51		

Discussion

To maintain the normal structure of the tissue and its functioning, optimal interaction of the cells is necessary both among themselves and with the extracellular matrix. Collagens and glycosaminoglycans are necessary for the development of cervical tissue [7,12,16]. With the development of pathology, the degradation products of the intercellular matrix and basement membranes have a remodeling effect on such cellular processes of tissue functioning as apoptosis, differentiation, migration, adhesion, angiogenesis and the immune response, being key mechanisms of pathogenesis [11,12,21,22,23,26]. A wide range of physiological and pathological effects of MMT makes them an attractive object for genetic studies of the molecular mechanisms of the development of cervical neoplasia [7,20].

The main among collagenases is matrix type 1 metalloproteinase (MMP-1) or interstitial collagenase, which provides degradation of type I, II, and III collagens [11,15,18,22].

An analysis of published data indicates the great scientific and practical importance of studying the genetic markers of MMP-1 for the molecular biological characteristics of the degradation of the intercellular matrix, determining the genetic markers of tumor cells that are important in the pathogenesis of development and in the prognosis of the disease.

The level of expression of MMP1 depends on single nucleotide polymorphic variants in regulatory regions of genes (promoters). The most studied single-nucleotide polymorphic variant of the MMP1 gene includes the polymorphic locus 1607 1G / 2G rs 1799750 with additional guanine (1G → 2G). 1G polymorphism is considered a “normal” allele; carriage of a 2G allele is a pathological mutation associated with inflammatory and oncological pathology.

The relationship of the polymorphism of the MMP1 1607 1G / 2G gene with the oncological pathology of the female reproductive system was established. So, the role of MMP -1 (1G / 2G) polymorphism in uterine fibroids was shown. In this case, the carriage of the homozygous genotype MMP-1 (1G / 1G-1607) is a prognostic marker for the favorable clinical course of uterine fibroids. Carriage of the 2G allele in heterozygous (1G / 2G-1607) or homozygous (2G / 2G-1607) forms promotes rapid growth and the development of multinodular forms of breast tumors [5]. The role of MMP-1 expression in the modification of the intercellular matrix in tumor progression and tumor angiogenesis in soft-tissue tumors,

fibromatosis, and sarcoma was revealed [21]. Significant expression of MMP-1 and MMP-2 is recorded in squamous cell carcinoma of the cervix [15,16]. Accelerated tumor growth is associated with a higher frequency of the MMP1 2G allele and multifocal growth [13,14]. In addition, the MMP1 2G allele was more common in patients with adenomyosis [17]. MMP1 is a potential risk marker for myometrial and endometrial hyperplasia [17]. It was shown that the bulk density of inflammatory cell infiltrate and the severity of dysplastic changes in cervical neoplasia and microinvasive carcinoma are associated with an increase in the expression of metalloproteinases-2, -3, -7 [12]. Carriage of the 2G allele of the MMP1 gene is involved in the pathogenesis of external genital endometriosis [3].

Our studies are consistent with the above data, a statistically significant association of 2G allele carriage with a risk of developing CIN ($\chi^2 = 15.4$; $P \leq 0.001$) and unreliable with carriage of the heterozygous genotype 1G / 2G ($\chi^2 = 1.4$; $P \geq 0.243$) were established. In the control group of patients, a statistically significant predominance of the 1G allele ($\chi^2 = 29.4$; $P \leq 0.001$) and the homozygous genotype 1G / 1G ($\chi^2 = 19.6$; $P \leq 0.001$) was found. The highest values of the carriage of the 2G allele and homozygous genotype 2G / 2G were found at CIN and at CIN III. Thus, the study of polymorphism of the MMP1 1607 1G / 2G gene is promising for predicting the course of cervical intraepithelial neoplasia and can be used to form risk groups for the development of this pathology.

References:

- [1] Bayramova G. R., Amirkhanyan A. S., Baranov I. I., Burmenskaya O. V., Kalinina E. A., Pripitnevich T. V., Bobrov M. Yu., Bunyaeva E. S. Chronic cervicitis associated with papillomavirus infection: diagnosis and management of patients // Doctor.Ru. 2017. No. 3 (132). S. 66–72.
- [2] Zhukova A.B. Squamous intraepithelial lesions of the cervix: a modern view of etiology, pathogenesis, diagnosis // Journal of Obstetrics and Women's Diseases. - 2019.-N 6. - P.87-98.
- [3] Ilyina A.R., Mironova E.S., Linkova N.S., Polyakova V.O., Kvetnoy I.M., Belushkina N.N. Matrix metalloproteinases as one of the links in the pathogenesis of external genital endometriosis // Uspekhi Fiziologicheskikh Nauk. - 2019.-N 4. -P.81-86.
- [4] Kugaevskaya E.V., Timoshenko O.S., Gureeva T.A., Solovieva N.I. The role of stromal proteolytic systems in tumor progression (review) // General resuscitation. - 2019.-N 5.- P.106-126
- [5] Letunovskaya A.V., Oleinikov D.A. Porebskaya O.Ya. Toropova Ya.G., The role of extracellular matrix in the pathogenesis of breast tumors // Cytology. - 2020.-N 2. -P.98-111.
- [6] Markelova EV, Zdor VV, Romanchuk A.L., Birko O.N. Matrix metalloproteinases, their relationship with the cytokine system, diagnostic and prognostic potential // Immunopathology, Allergology, Infectology. - 2016 N ° 2. - S.11 -23.
- [7] Nazhmutdinova D. K., Yuldasheva D. Yu. Clinical significance of the determination of matrix metalloproteinases and their inhibitors in endometrial hyperplasia combined with cervical pathology // West. Tashkent honey. academy. - Tashkent, 2014. - No. 4. - S. 86-89 (14.00.00; No. 13).
- [8] Nazarova N.M., Pavlovich S.V., Attoeva D.I. HPV-associated diseases in women and men: principles of diagnosis, treatment, prevention // Medical Council. - 2019. - No. 7. - S. 82-86. DOI: <https://doi.org/10.21518/2079-701X-2019-7-82-86>.
- [9] Novik V. I. Clarifying cytological diagnosis of cervical intraepithelial neoplasia of the cervix using microimaging // Tumors of the female reproductive system 2019; 15 (3): 24–31

- [10] Protasova A.E. Cervical intraepithelial neoplasia and cervical cancer. Is human papillomavirus the only risk factor? // Effective pharmacotherapy. -2019. T. 15. No. 32. S. 42–46.
- [11] 2. Rudenko K.A., Tuguz A.R. The pathophysiological role of insertion (1607 INS G) of the matrix metalloproteinase gene in airway remodeling in bronchial asthma // Vyatka Medical Bulletin. - 2019.-N 3. -P.43-45.
- [12] 3. Selyakova M.S., Ageeva T.A., Savchenko S.V. The relationship between the expression of metalloproteinases and TIMP1 with the severity of inflammatory infiltration in the cervix in women of different age groups with intraepithelial neoplasia and microinvasive carcinoma // Siberian Oncological Journal. 2019 18 (6): 50–56. - doi: 10.21294 / 1814-4861-2019-18-6-50-56.
- [13] 4. Solovyova N.I., Timoshenko O.S., Gureeva T.A., Kugaevskaya E.V. Matrix metalloproteinases and their endogenous regulators in squamous cell carcinoma of the cervix uteri: (review of own data) // Biomedical chemistry. - 2015. - Volume 61, No. 6, p. 694-704 DOI
- [14] 5. Solovyova N.I., Timoshenko O.S., Gureeva T.A., Kugaevskaya E.V., Zavalishina L.E., Andreeva Yu.Yu., Solovieva N.I. Solovyova N.I. Tissue collagenase MMP-14 and endogenous regulators of its activity in the uterine body with squamous cell carcinoma of the cervix uteri // Archive of Pathology. - 2017. - Publisher Media Sphere (M.), Volume 79, No. 6, p. 36-42 DOI
- [15] 6. Timoshenko O.S., Gureeva T.A., Kugaevskaya E.V., Zavalishina L.E., Andreeva Yu.Yu., Solovyova N.I. Expression of EMMPRIN and MMP-1 matrix metalloproteinase in the cervix and uterine body with cervical squamous cell carcinoma // Archive of Pathology. - 2019.-N 6. -P.34-40.
- [16] 7. Timoshenko O. S., Gureeva T. A., Kugaevskaya E. V., Zavalishina L. E., Andreeva Yu. Yu., Solovieva N. I., Gelatinases A. V. Endogenous regulators in the uterine body with squamous uterine cervical carcinoma / [et al.] // Arch. pathology. - 2018. - Volume 80, N 6. - S. 22-28.
- [17] 8. Chukhlovin AB, Totolyan Areg A. Biological effects of myometrial hyperplasia: the role of clinically significant gene variants // Molecular Medicine. - 2014. - No. 4. - S.14 - 29.
- [18] 9. Shadrina AS, Plieva YaZ, Kushlinsky DN, Morozov AA, Filipenko ML, Chang VL, Kushlinsky NOT. Classification, regulation of activity, genetic polymorphism of matrix metalloproteinases in normal and pathological conditions // Clinical medicine almanac. 2017; 45 (4): 266–79. doi: 10.18786 / 2072-0505-2017-45-4-266-279.
- [19] 10. Yuldasheva D. Yu., Nazhmutdinova D. K. The role of genetic factors in predicting the risk of developing intraepithelial neoplasia of the cervix uteri // Tomsk State University Journal. Tashkent honey. academy. - Tashkent, 2015. - No. 1. - S. 9-11. (14.00.00; No. 13).
- [20] 11. Yarmolinskaya M.I., Molotkov A.S., Denisova V.M. Matrix metalloproteinases and inhibitors: classification, mechanism of action. Journal of Obstetrics and Women's Diseases. 2012; 61, 1: 113-25.
- [21] Bodner K., Kimberger O., Czewenka K. et al. MMP-1 and MMP-2 expression in uterine leiomyosarcoma and correlation with different clinicopathologic parameters // J of the Society for Gynecol. Invest. - 2003. - N10. - P. 443-446.
- [22] Huang HL, Wu S, Hsu LA, Teng MS, Lin JF, Sun YC, Ko YL. Genetic variants associated with circulating MMP1 levels near matrix metalloproteinase genes on chromosome 11q21-22 in Taiwanese: interaction with obesity. BMC Med Genet. 2013; 14:30. doi: 10.1186/1471-2350-14.

- [23] Alexander A., Kozin Sergey A. N-domain of angiotensin-converting enzyme hydrolyzes human and rat amyloid- β (1-16) peptides as arginine specific endopeptidase potentially enhancing risk of Alzheimer's disease // Scientific reports, издательство Nature Publishing Group (United Kingdom), 2018. - том 8, с. 298 DOI
- [24] Roebuck M.M., Helliwell T.R., Chaudhry I.H. et al. Matrix metalloproteinase expression is related to angiogenesis and histologic grade in spindle cell soft tissue neoplasms of the extremities // Am. J Clin. Pathol. - 2005. - Vol. 123. - P. 405 - 414.
- [25] Sri Manjari K, Nallari P, Balakrishna N, Vidyasagar A, Prabhakar B, Jyothy A, Venkateshwari A. Influence of matrix metalloproteinase-1 gene -1607 (1G/2G) (rs1799750) promoter polymorphism on circulating levels of MMP-1 in chronic pancreatitis. Biochem Genet. 2013;51(7-8): 644-54. doi: 10.1007/s10528-013-9594-9.
- [26] Trombone AP, Cavalla F, Silveira EM, Andreo CB, Francisconi CF, Fonseca AC, Letra A, Silva RM, Garlet GP. MMP1-1607 polymorphism increases the risk for periapical lesion development through the upregulation MMP-1 expression in association with pro-inflammatory milieu elements. J Appl Oral Sci. 2016;24(4): 366-75. doi: 10.1590/1678-775720160112.