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GENETIC DETERMINANTS OF HYPERPLASTIC DISEASES OF THE ENDOMETRIUM AND MAMMARY GLANDS

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Summary.

Genetic predisposition constitutes a well-established etiological factor in the pathogenesis of proliferative diseases of the mammary gland and uterus. Empirical evidence from cytogenetic and epidemiological studies substantiates a heritable component in the development of uterine hyperplastic processes (UHPP).

Objective. *The aim of our study was to investigate the significance of rs1138272 polymorphisms in the GSTP1 (Ala/Val) gene and rs5918 polymorphisms in the ITGB3 (T/C) gene in the mechanisms underlying the development of hyperplastic processes of the endometrium and/or myometrium, concomitant with benign breast dysplasia in perimenopausal women.*

Methods. *A total of 82 patients with a confirmed diagnosis of endometrial and/or myometrial hyperplastic processes were enrolled. In addition to standard diagnostic protocols for uterine hyperplastic conditions, all study participants underwent genetic analysis. The study cohort was divided into a main group (n=50) of patients with UHPP and co-existing benign breast dysplasia, and a comparison group (n=32) of patients with UHPP without breast pathology. The control group consisted of 80 clinically healthy women. The principles of bioethics, approved by the Scientific Council of Samarkand State Medical University, are preserved and upheld in full compliance. To variationally estimate the frequency of genotypes of the studied rs 5918 polymorphism in the ITGB3 gene (T/C), the agreement was analyzed between the expected (H_{exp}) and observed (H_{obs}) frequencies of their distribution in the groups of patients with UHPP and controls, in accordance with the Hardy-Weinberg equilibrium (PXB, p>0.05). The work was carried out within the framework of the scientific project No. 012000260 «Development of promising technologies for the prevention, diagnostics, and treatment of infectious and non-infectious diseases of the human body that have social significance» in accordance with the research plan of Samarkand State Medical University.*

Results. *In the main group, the expected (Hexp) and observed (Hobs) frequencies of the T/T, T/C, and C/C genotypes for rs5918 in the ITGB3 gene (T/C) were 0.85 and 0.86 (χ2=0.00), 0.15 and 0.14 (χ2=0.07), and 0.00 and 0.01 (χ2=0.44), respectively, with no statistically significant differences (p=0.45). In the control group, the frequencies were: 0.83 and 0.83 (χ2=0.01), 0.18 and 0.16 (χ2=0.12), and 0.00 and 0.10 (χ2=0.61), also without significant differences (p=0.37).*

Discussion. *The findings suggest that the rs5918 polymorphism in the ITGB3 gene is not a principal driver mutation in the pathogenesis of hyperplastic diseases of the uterus and mammary glands. Furthermore, within the subgroup of patients with UHPP, no association was identified between this polymorphism and concomitant breast pathology. However, among patients who presented with abnormal uterine bleeding (AUB), the heterozygous T/C genotype was significantly more common.*

Conclusion. *A solitary genetic polymorphism may exert a negligible effect on complex physiological systems; however, the aggregate effect of alterations in multiple genes can significantly disrupt systemic homeostasis and precipitate pathological states. Consequently, the investigation of genetic susceptibility to multifactorial diseases necessitates the evaluation of polygenic models or the analysis of multiple polymorphisms within pertinent gene pathways.*

Keywords: *Polymorphism; Uterine Hyperplastic Processes; Mammary Gland.*

Introduction

Genetic predisposition represents a well-established factor in the pathogenesis of proliferative disorders affecting both the mammary glands and uterus [1-3]. Substantial cytogenetic and epidemiological evidence supports the heritable nature of uterine hyperplastic processes (UHPP) [1-3].

Genetic investigations have demonstrated aberrant local expression of numerous growth factors and cytokines, indicating a potential genetic susceptibility to the combined development of endometrial and mammary gland pathology [4,5].

Research conducted by Romaniuk et al. examined the pathogenetic relationship between myometrial, endometrial, and mammary gland disorders at both endocrine-metabolic and genetic levels, identifying steroid receptors as crucial mediators in these processes [6].

Reduced expression of specific tumor invasion and metastasis suppressor genes correlates with unfavorable clinical prognosis and appears in low-grade malignancies. Among cell adhesion molecules, integrins represent molecules of particular interest [7,8].

Hyperestrogenism is hypothesized to significantly influence gene expression patterns, modifying cellular signaling regulation and contributing to hyperplastic process development. This regulatory mechanism involves multiple genes, as supported by their chromosomal localization data [9-11].

Apoptosis occurs primarily during the late secretory phase and menstruation, while being substantially absent during proliferation and early secretory phases of the endometrial cycle [12].

The survivin protein, encoded by the disease genome, functions as a member of the of the inhibitor of apoptosis protein family and demonstrates ubiquitous cellular expression, participating in essential biological processes including angiogenesis and cell division [13,14].

UHPP demonstrates frequent comorbidity with benign breast dysplasia (BBD), with reported co-occurrence rates of 60-65% [15]. The etiological factors underlying hyperplastic processes are multifactorial and diverse, though their developmental mechanisms, particularly associations

with molecular genetic factors, remain incompletely characterized [16-18]. An integrated research approach may elucidate novel aspects of the relationship between UHPP and BBD pathogenesis, potentially facilitating individualized patient management strategies, enhancing treatment efficacy, and improving quality of life while reducing reliance on complex surgical interventions [19]. Contemporary preventive medicine emphasizes determining pathology risk through identification of significant genetic determinants.

Objective

The aim of our study was to investigate the potential association of rs1138272 polymorphisms in the GSTP1 (Ala/Val) gene and rs5918 polymorphisms in the ITGB3 (T/C) gene and the development of hyperplastic processes involving the endometrium, myometrium, and mammary glands in perimenopausal women.

Examination methods

A total of 82 patients with a confirmed diagnosis of endometrial and/or myometrial hyperplastic processes were enrolled. In addition to the standard diagnostic workup for uterine hyperplastic conditions, all participants underwent genetic analysis.

The main study group comprised 50 patients presenting with hyperplastic processes of the endometrium and/or myometrium combined with benign breast dysplasia. The comparison group included 32 patients with UHPP without concomitant breast pathology. The control group consisted of 80 ostensibly healthy women.

The principles of bioethics, approved by the Scientific Council of Samarkand State Medical University, are preserved and upheld in full compliance.

To variationally estimate the frequency of genotypes of the studied rs 5918 polymorphism in the ITGB3 gene (T/C), the agreement was analyzed between the expected (H_{exp}) and observed (H_{obs}) frequencies of their distribution in the groups of patients with UHPP and controls, in accordance with the Hardy-Weinberg equilibrium (PXB, p>0.05).

The work was carried out within the framework of the scientific project No. 012000260 «Development of promising technologies for the prevention, diagnostics, and treatment of infectious and non-infectious diseases of the human body that have social significance» in accordance with the research plan of Samarkand State Medical University.

The results of the study

In the main group of c patients, the expected (Hexp) and observed (Hobes) frequencies of the T/T, T/C, and C/C polymorphisms of rs 5918 in the ITGB3 gene (T/C) were 0.85 and 0.86 ($\chi2$=0.0); 0.15 and 0.14 ($\chi2$=0.07); 0.0 and 0.01 ($\chi2$=0.44), respectively, with an unreliable difference in results (p=0.45).

In the control group, the expected (H_{exp}) and observed (H_{obs}) frequencies of the T/T, T/C, and C/C polymorphism rs 5918 in the ITGB3 gene (T/C) corresponded to the values 0.83 and 0.83 ($\chi2$=0.01); 0.18 and 0.16 ($\chi2$=0.12); 0.0 and 0.1 ($\chi2$=0.61), respectively, also with an unreliable difference in the results obtained (p=0.37) (table 1).

The index of heterozygosity in terms of observed (Hobs) and expected (Hexp) parameters in the main group of patients with UHPP for the rs 5918 polymorphism in the ITGB3 gene (T/C) practically did not differ from those in the control group (0.15 and 0.14 versus 0.18 and 0.16, respectively; D was 0.08 and 0.1).

Table 1

Analysis of the expected (Hexp) and observed (Hobs) frequency of distribution of rs5918 polymorphism genotypes in the ITGB3 gene (T/C) by PXB in the control group

Alleles	Frequency of alleles				
T	0.91				
C	0.09				
Genotypes	Frequency of genotypes		X^2	P	df
	H_{exp}	H_{obs}			
T/T	0.83	0.83	0.01	0.37	1
T/C	0.18	0.16	0.12		
C/C	0.0	0.1	0.61		
Total	1.00	1.00	0.74		

A comparable genotypic distribution pattern was observed with respect to the expected (H_{exp}) and observed (H_{obs}) frequencies of the T/T, T/C and C/C polymorphism rs 5918 in the ITGB3 gene (T/C) in the main group and the comparison group. Specifically, in the comparison group, frequencies were: 0.81 and 0.82 ($\chi2$=0.0); 0.19 and 0.17 ($\chi2$=0.06); 0.0 and 0.01 ($\chi2$=0.28) with an unreliable difference (p=0.53), whereas in the main group they had values of 0.88 and 0.88 ($\chi2$=0.0); 0.12 and 0.11 ($\chi2$=0.02); 0.0 and 0.0 ($\chi2$=0.18) with a difference equal to p=0.62 (Table 2, 3).

The heterozygosity index values for the observed (H_{obs}) and expected (Hexp) parameters in the comparison group for the rs 5918 polymorphism in the ITGB3 gene (T/C) relative to the control were 0.19 and 0.17 versus 0.18 and 0.16, respectively (D was 0.1 and 0.1). In the main group of patients with UHPP and BBD, these parameters compared to the control were 0.12 and 0.11 (D=0.06) versus 0.18 and 0.16 (D=0.1), respectively.

Our analysis of the frequency distribution of alleles and genotypes of the polymorphic variant rs 5918 in the ITGB3 (T/C) gene in the group of ostensibly healthy donors allowed us to establish the following: the frequency of the T allele was 91.2%, and the C allele was 8.8%. At the same time, the carriage of the homozygous TB genotype was determined in 82.5% (n=66), the heterozygous genotype (HC) in 17.5% (n=14), and no homozygous mutant genotype was detected in either the main or control group (table 4).

Table 2

Analysis of the expected and observed distribution frequencies of rs5918 polymorphism genotypes in the ITGB3 gene (T/C) in the comparison group

Alleles	Frequency of alleles				
T	0.91				
C	0.09				
Genotypes	Frequency of genotypes		χ^2	P	df
	$^*H_{exp}$	$^*H_{obs}$			
T/T	0.81	0.82	0.0	0.53	1
T/C	0.19	0.17	0.06		
C/C	0.0	0.01	0.28		
Total	1.00	1.00	0.34		

Table 3

Analysis of expected and observed distribution frequencies of rs5918 polymorphism genotypes in the ITGB3 (T/C) gene in the main group

Alleles	Frequency of alleles				
T	0.94				
C	0.06				
Genotypes	Frequency of genotypes		χ^2	P	df
	$^*H_{exp}$	$^*H_{obs}$			
T/T	0.88	0.88	0.0	0.62	1
T/C	0.12	0.11	0.02		
C/C	0.0	0.0	0.18		
Total	1.00	1.00	0.2		

Table 4

The frequency of distribution of alleles and genotypes of the rs5918 polymorphism in the ITGB3 gene (T/S) between patients with hyperplastic processes and the control group

Group	n	Frequency of alleles				Frequency of genotype distribution					
		T		C		T/T		T/C		C/C	
		n	%	n	%	n	%	n	%	n	%
A group of patients with hyperplastic processes of the endometrium and/or myometrium	82	152	92.7	12	7.3	70	85.4	12	14.6	0	0
Main group	50	94	94.0	6	6.0	44	88.0	6	12.0	0	0
Comparison group	32	58	90.6	6	9.4	26	81.2	6	18.8	0	0
Control group	80	146	91.2	14	8.8	66	82.5	14	17.5	0	0

Subsequently, we analyzed the allele and genotype frequency distribution of the rs 5918 polymorphism in the ITGB3 (T/C) gene in a combined group of patients with UHPP. The T allele frequency was 92.7% (n=152), and the C allele frequency was 7.3% (n=12). The frequency of carriage of the homozygous T/T genotype was 85.4% (n=70), the heterozygous T/C genotype was 14.6% (n=12), and no homozygous mutant C/C genotype was detected.

Additionally, we performed a comparative analysis of of allele and genotype frequencies in the group of patients with solely uterine hyperplastic processes (comparison group). In this group, the T allele frequency was 90.6% (n=58), and the C allele frequency was 9.4% (n=6). The homozygous T/T genotype was present in 81.2% (n=26) of cases, and the heterozygous T/C genotype in 18.8% (n=6) cases, whereas in the main group of patients with BD, the T allele was registered in 94% (n=94.0), and the C allele in 6.0% (n=6) cases. The carriage of the homozygous T/T genotype was determined in 88% (n=44), the heterozygous T/C genotype in 12% (n=6) cases.

The evaluation of the frequency distribution of alleles and genotypes of the rs 5918 polymorphism in the ITGB3 (T/C) gene demonstrated that in the combined UHPP group of patients, the proportion of T and C alleles were virtually identical to those in the ostensibly healthy donor group (χ2=0.2; p=0.7; OR=1.2; 95%CI: 0.44-2.36).A similar pattern was observed for genotype distribution: T/T (χ2=0.2; p=0.7; OR=1.2; 95%CI:0.43-2.48), T/S (χ2=0.2; p=0.7; OR=0.8; 95%CI:0.35-2.0). The mutant C/C genotype was not observed in patients with endometrial and/or myometrial hyperplastic processes or in the control group. These findings no significant differences in allele or genotype frequency distribution of the rs918 polymorphism in the ITGB3 (T/C) gene between patients with UHPP and ostensibly healthy donors (table 5).

Table 5

The frequency of distribution of alleles and genotypes of the rs5918 polymorphism in the ITGB3 gene (T/S) between patients with hyperplastic processes and the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Patients with uterine hyperplastic processes		Control group						
	n	%	n	%					
T	152	92.7	146	91.3	0.2	0.70	1.0	0.44-2.36	1.2
C	12	7.3	14	8.8	0.2	0.70	1.0	0.47-2.05	0.8
T/T	70	85.4	66	82.5	0.2	0.70	1.0	0.43-2.48	1.2
T/C	12	14.6	14	17.5	0.2	0.70	0.8	0.35-2	0.8

Subsequent assessment of the allele and genotype frequency distribution for the studied genetic polymorphism in the main and comparison groups similarly established no significant differences relative to the control group: in the comparison group, the T and C allele frequencies (χ^2=0.0; p=0.9; OR=0.9; 95% CI: 0.25-3.95), frequency of genotypes T/T (χ^2=0.0; p=0.9; OR=0.9; 95% CI: 0.23-4.24), T/C (χ^2=0.0; p=0.9; OR=1.1; 95% CI: 0.25-4.61) (table 6); in the main group, the T and C allele frequencies (χ^2=0.7; p=0.5; OR=1.5; 95% CI: 0.56-4.02), genotype frequency T/T (χ^2=0.7; p=0.4; OR=1.6; 95% CI: 0.56-4.33), T/C (χ^2=0.7; p=0.4; OR=0.6; 95% CI: 0.23-1.79) (table 7).

Table 6

Frequency of distribution of allele frequencies and genotypes of the rs5918 polymorphism in the ITGB3 gene (T/S) between the comparison group and the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Comparison Group		Control group						
	n	%	n	%					
T	58	90.6	146	91.3	0.0	0.90	1.0	0.25-3.95	0.9
C	6	9.4	14	8.8	0.0	0.90	1.0	0.56-1.81	1.1
T/T	26	81.3	66	82.5	0.0	0.90	1.0	0.23-4.24	0.9
T/C	6	18.8	14	17.5	0.0	0.90	1.1	0.25-4.61	1.1

Table 7

The frequency of distribution of allele frequencies and genotypes of the rs5918 polymorphism in the ITGB3 gene (T/C) between the main group and the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Comparison Group		Control group						
	n	%	n	%					
T	94	94.0	146	91.3	0.7	0.50	1.0	0.27-3.97	1.5
C	6	6.0	14	8.8	0.7	0.50	1.0	0.53-1.76	0.7
T/T	44	88.0	66	82.5	0.7	0.40	1.1	0.27-4.27	1.6
T/C	6	12.0	14	17.5	0.7	0.40	0.7	0.17-2.74	0.6

We subsequently evaluated the allele and genotype frequency distributions between the main group and the comparison group. Consistent with the aforementioned results, no significant differences were identified in the distribution of T and C alleles. (χ^2=0.7; p=0.5; OR=0.6; 95% CI: 0.3-3.13), and T/T (χ^2=0.7; p=0.4; OR=0.6; 95% CI: 0.26-3.25), T/C (χ^2=0.7; p=0.4; OR=1.7; 95% CI: 0.44-5.51) genotypes (table 8).

Table 8

Analysis of differences in the frequency distribution of alleles and genotypes of the rs5918 polymorphism in the ITGB3 (T/C) gene between the main group and the comparison group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Main group		Comparison Group						
	n	%	n	%					
T	94	94.0	58	90.6	0.7	0.50	1.0	0.3-3.13	0.6
C	6	6.0	6	9.4	0.7	0.50	1.0	0.33-3.23	1.6
T/T	44	88.0	26	81.3	0.7	0.40	0.9	0.26-3.25	0.6
T/C	6	12.0	6	18.8	0.7	0.40	1.6	0.44-5.51	1.7

Given that the ITGB3 gene encodes the amino acid sequence of the platelet fibrinogen receptor protein molecule, we conducted an analysis of allele and genotype distribution in patients presenting with AUB (table 9).

Table 9

Distribution of alleles and genotype of the rs5918 polymorphism in the ITGB3 (T/C) gene in patients who were admitted for examination with complaints of bleeding

Group	n	Frequency of alleles				Frequency of genotype distribution					
		T		C		T/T		T/C		C/C	
		n	%	n	%	n	%	n	%	n	%
The main group of patients	82	152	92.7	12	7.3	70	85.4	12	14.6	0	0
Patients with bleeding symptoms	69	128	92.5	5	7.2	58	84.1	11	15.9**	0	0
Patients without bleeding	13	24	92.3	1	7.7	12	92.3	1	7.7	0	0

Note:
** – p <0.05 the significance of differences between groups I and II*
*** – p <0.001 the significance of differences between groups I and II*

Investigation of allelic and genotypic frequencies of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene in perimenopausal patients with uterine and mammary gland hyperplastic processes revealed the following heterozygosity indices: in the main group, the observed (H_{obs}) and expected (H_{exp}) parameters for the rs1138272 polymorphism in the GSTP1 gene (Ala/Val) were 0.13 and 0.13 (D=0.07), compared to 0.1 and 0.12 (D= –0.15) in the control group (Table 10).

Table 10

Analysis of the expected (Hexp) nd observed (Hobs) frequency of distribution of rs1138272 polymorphism genotypes in the GSTP1 (Ala/Val) gene by PXB in the control group

Alleles	Frequency of alleles				
Ala	0.94				
Val	0.06				
Genotypes	Frequency of genotypes		χ^2	P	df
	H_{exp}	H_{obs}			
Ala/Ala	0.87	0.88	0.01	0.82	1
Ala/Val	0.1	0.12	0.2		
Val/Val	0.01	0.0	1.51		
Total	1.00	1.00	1.72		

In patients of the main group and in the comparison group, the expected (H_{exp}) and observed (H_{obs}) frequencies of the Ala/Ala, Ala/Val, and Val/Val polymorphisms of rs1138272 in the GSTP1 (Ala/Val) gene demonstrated the following distributions: in the comparison group, they had values of 0.81 and 0.82 ($\chi2$=0.0); 0.19 and 0.17 ($\chi2$=0.06); 0.0 and 0.01 ($\chi2$=0.28) no statistically significant deviation (p=0.53); in the main group of (H_{exp}) and (H_{obs}), the frequencies of the studied genotypes corresponded to values of 0.9 and 0.9 ($\chi2$=0); 0.1 and 0.1 ($\chi2$=0.01); 0.0 and 0.0 ($\chi2$=0.13) with a a deviation significance of p=0.7 (table 11, 12).

In the control group, the proportion of the Ala allele was 93.7% (n=150), and the Val allele was 6.2% (n=10). Concurrently, the proportion of the homozygous Ala/Ala genotype was 88.7% (n=71), and the heterozygous Ala/Val genotype was 10.0% (n=8). It should be noted that, similarly to the previously studied rs1138272 polymorphism in the GSTP1 (Ile/Val) gene, in this analysis, the presence of a mutant homozygous genotype (Val/Val) was also identified, which was recorded in one case, constituting 1.2% (table 13).

Analysis of the allele and genotype distribution of the rs17576 polymorphism of the rs1138272 gene in the GSTP1 (Ala/Val) gene in the group of patients with UHPP revealed the Ala allele in 93.3% (n=153), and the Val allele in 6.7% (n=11). The homozygous Ala/Ala genotype was registered in 86.6% (n=71) of cases, the heterozygous Ala/Val genotype in 13.4% (n=11) of cases, and no homozygous mutant Val/Val genotype was detected in the UHPP patient group.

Table 11

Analysis of the expected (Hexp) nd observed (Hobs) frequency of distribution of rs1138272 polymorphism genotypes in the GSTP1 (Ala/Val) gene by PXB in the comparison group

Alleles	Frequency of alleles				
Ala	0.91				
Val	0.09				
Genotypes	Frequency of genotypes		χ^2	P	df
	*H_{exp}	*H_{obs}			
Ala/Ala	0.81	0.82	0.0	0.5	1
Ala/Val	0.19	0.17	0.06		
Val/Val	0.0	0.01	0.28		
Total	1.00	1.00	0.34		

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Table 12

Analysis of the expected (Hexp) nd observed (Hobs) frequency of distribution of rs1138272 polymorphism genotypes in the GSTP1 (Ala/Val) gene by PXB in the main group

Alleles	Frequency of alleles				
Ala	0.95				
Val	0.05				
Genotypes	Frequency of genotypes		χ^2	P	df
	*H_{exp}	*H_{obs}			
Ala/Ala	0.9	0.9	0	0.7	1
Ala/Val	0.1	0.1	0.01		
Val/Val	0.0	0.0	0.13		
Total	1.00	1.00	0.14		

Table 13

The frequency of distribution of alleles and genotypes of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene in the group of conditionally healthy donors and in patients with UHPP and BBD

Group	n	Frequency of alleles				Frequency of genotype distribution					
		Ala		Val		Ala/Ala		Ala/Val		Val/Val	
		n	%	n	%	n	%	n	%	n	%
A group of patients with hyperplastic processes of the endometrium and/ or myometrium	82	153	93.3	11	6.7	71	86.6	11	13.4	0	0
Main group	50	95	95.0	5	5.0	45	90.0	5	10.0	0	0
Comparison group	32	58	90.6	6	9.4	26	81.2	6	18.7		0
Control group	80	150	93.7	10	6.2	71	88.7	8	10.0	1	1.2

A comparative analysis of allele and genotype frequency distribution was conducted between the main and comparison groups. In the comparison group patients, the proportion of the Ala allele was 90.6% (n=58), and the Val allele was 9.4% (n=6). The homozygous Ala/Ala genotype was detected in 81.2% (n=26) of cases, while the heterozygous Ala/Val genotype was present in 18.7% (n=8) of cases.

Evaluation of the allele and genotype frequency distribution of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene demonstrated that in the combined UHPP group, the proportion of Ala and Val alleles were virtually identical to those in the in the ostensibly healthy donor control group (control) ($\chi2$=0.0; p=0.9; OR=0.9; 95%CI: 0.43-2.28). A similar pattern was observed for genotype distributions: Ala/Ala ($\chi2$=0.2; p=0.7; OR=0.8; 95%CI:0.42-2.26), Ala/Val ($\chi2$=0.5; p=0.5; OR=1.4; 95%CI:0.59-3.04). These findings indicate no significant differences in the allele and genotype frequency distribution of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene between patients with endometrial and/or myometrial hyperplastic processes and ostensibly healthy donors (table 14).

Subsequent assessment of the allele and genotype frequency distribution for the studied genetic polymorphism in the main group and in the comparison group also established no significant differences relative to the control group: in the comparison group, the frequency of alleles Ala and Val (χ^2=0.; p=0.5; OR=0.6; 95% CI: 0.26-3.59), frequency of genotypes Ala/Ala (χ^2=1.1; p=0.3; OR=0.5; 95% CI: 0.23-3.62), Ala/Val (χ^2=1.6; p=0.3; OR=2.1; 95% CI: 0.49-7.23) (table15); in the main group, the frequency of alleles Ala and Val (χ^2=0.2; p=0.7; OR=1.3; 95% CI: 0.24-4.26), frequency of genotypes Ala/Ala (χ^2=0.1; p=0.9; OR=1.1; 95% CI: 0.24-4.32), Ala/Val (χ^2=0.0; p=1.0; OR=1.0; 95% CI: 0.24-4.14) (table 16).

Table 14

Analysis of differences in the frequency distribution of alleles and genotypes of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene between a group of UHPP patients and conditionally healthy donors.

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Patients with uterine hyperplastic processes		Control group						
	n	%	n	%					
Ala	153	93.3	150	93.8	0.0	0.90	1.0	0.43-2.28	0.9
Val	11	6.7	10	6.3	0.0	0.90	1.0	0.41-2.49	1.1
Ala/Ala	71	86.6	71	88.8	0.2	0.70	1.0	0.42-2.26	0.8
Ala/Val	11	13.4	8	10.0	0.5	0.50	1.3	0.59-3.04	1.4

Table 15

Analysis of differences in the allele and genotype frequency distribution of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene between the comparison group and the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Comparison Group		Control group						
	n	%	n	%					
Ala	58	90.6	150	93.8	0.7	0.50	1.0	0.26-3.59	0.6
Val	6	9.4	10	6.3	0.7	0.50	1.0	0.48-2.22	1.6
Ala/Ala	26	81.3	71	88.8	1.1	0.30	0.9	0.23-3.62	0.5
Ala/Val	6	18.8	8	10.0	1.6	0.30	1.9	0.49-7.23	2.1

Table 16

Analysis of differences in the allele and genotype frequency distribution of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene between the main group and the control group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Main group		Control group						
	n	%	n	%					
Ala	95	95.0	150	93.8	0.2	0.70	1.0	0.24-4.26	1.3
Val	5	5.0	10	6.3	0.2	0.70	1.0	0.48-2.04	0.8
Ala/Ala	45	90.0	71	88.8	0.1	0.90	1.0	0.24-4.32	1.1
Ala/Val	5	10.0	8	10.0	0.0	0.99	1.0	0.24-4.14	1.0

The allele and genotype frequency distributions between the main group and the comparison group were also evaluated. Alleles Ala and Val ($\chi2$=1.2; p=0.3; OR=0.5; 95% CI: 0.31-2.95), genotypes Ala/Ala ($\chi2$=1.3; p=0.3; OR=0.5; 95% CI: 0.27-3.04), Ala/Val ($\chi2$=1.3; p=0.3; OR=2.1; 95% CI: 0.56-6.32) (table 17).

Table 17

Analysis of differences in the allele and genotype frequency distribution of the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene between the main group and the comparison group

Alleles and genotypes	Number of alleles and genotypes examined				χ2	p	RR	95%CI	OR
	Main group		Comparison group						
	n	%	n	%					
Ala	95	95.0	58	90.6	1.2	0.30	1.0	0.31-2.95	0.5
Val	5	5.0	6	9.4	1.2	0.30	1.0	0.29-3.81	2.0
Ala/Ala	45	90.0	26	81.3	1.3	0.30	0.9	0.27-3.04	0.5
Ala/Val	5	10.0	6	18.8	1.3	0.30	1.9	0.56-6.32	2.1

Discussion

The obtained results confirm the absence of a statistically significant association between carriage of the T and C alleles, as well as the T and T genotypes of the rs5918 polymorphism in the ITGB3 (T/C) gene, and the development of hyperplastic processes of the endometrium and/or myometrium. These findings can be explained by the fact that the rs5918 polymorphism in the ITGB3 (T/C) gene is not a driver mutation in the pathogenesis of hyperplastic diseases of the uterus and mammary glands. Furthermore, investigation of the combined patient group with UHPP from a similar perspective did not reveal any association between this polymorphism and the co-occurrence of this pathology with mammary glands diseases. During the examination of patients presenting with bleeding, the heterozygous T/C rs5918 genotype in the ITGB3 gene was significantly more prevalent among patients with bleeding manifestations. Consequently, detection of the heterozygous genotype in the ITGB3 gene in blood serum may indicate potential bleeding predisposition and risk of bleeding recurrence.

Conclusion

The obtained results confirm the absence of a significantly significant association between the carriage of the Ala and Val alleles, as well as the Ala/Ala, Ala/Val polymorphism rs1138272 in the GSTP1 (Ala/ Val) gene, and the development of uterine hyperplastic processes and breast diseases. These findings can be explained by the fact that the rs1138272 polymorphism in the GSTP1 (Ala/Val) gene does not represent a driver mutation for UHPP developmen. Additionally, it is necessary to consider that metabolic determinants operate through complex interactions, facilitating initiation, potentiation, or inhibition of individual system functions, as well as functional compensation between different pathways. An alteration in a single gene encoding a specific factor may not substantially impact the entire system; however, concurrent changes in multiple genes can fundamentally alter systemic processes and precipitate pathology. Therefore, when investigating genetic polymorphisms

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associated with specific pathological conditions, it is advisable to evaluate the influence of multiple genes or several polymorphism types within a single gene rather than isolated genetic variants.

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ГЕНЕТИЧНІ ДЕТЕРМІНАНТИ ГІПЕРПЛАЗИЧНИХ ЗАХВОРЮВАНЬ ЕНДОМЕТРІЮ ТА МОЛОЧНИХ ЗАЛОЗ

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Резюме.

Генетична схильність є загальновизнаним етіологічним фактором у патогенезі проліферативних захворювань молочної залози та матки. Емпіричні дані цитогенетичних та епідеміологічних досліджень підтверджують спадкову складову у розвитку гіперпластичних процесів матки.

Мета дослідження. Метою нашого дослідження було вивчення значення поліморфізмів rs1138272 в гені GSTP1 (Ala/Val) та поліморфізмів rs5918 в гені ITGB3 (T/C) у механізмах, що полягають в основі розвитку гіперпластичних процесів ендометрію та/або міометрію, що супроводжуються доброякісною дисплазією молочної залози у жінок в перименопаузі.

Матеріали і методи. Усього було включено 82 пацієнтки з підтвердженим діагнозом гіперпластичних процесів ендометрію та/або міометрію. На додаток до стандартних діагностичних протоколів гіперпластичних станів матки всі учасниці дослідження

пройшли генетичний аналіз. Досліджувана когорта була розділена на основну групу (n=50) пацієнток з гіперпластичними процесами матки та супутньою доброякісною дисплазією молочних залоз і групу порівняння (n=32) пацієнток з гіперпластичними процесами матки без патології молочних залоз. Контрольна група складалася з 80 клінічно здорових жінок.

Принципи біоетики, затверджені науковою радою Самаркандського державного медичного університету, збережені та дотримуються в повному обсязі.

Для варіаційної оцінки частоти генотипів досліджуваного поліморфізму rs 5918 в гені ITGB3 (T/C) було проаналізовано узгодженість між очікуваною (Hexp) та спостережуваною (Hobs) частотами їх розподілу в групах пацієнтів з УГПП та контрольних групах відповідно до рівноваги Харді-Вайнберга (РХВ, p>0,05).

Робота виконана у рамках наукового проекту № 012000260 «Розробка перспективних технологій профілактики, діагностики та лікування інфекційних та неінфекційних захворювань організму людини, що мають соціальне значення» відповідно до плану наукових досліджень Самаркандського державного медичного університету.

Результати дослідження. У основній групі очікувана (Hexp) та спостережувана (Hobs) частота генотипів T/T, T/C та C/C для rs5918 у гені ITGB3 (T/C) становила 0,85 та 0,86 ($\chi2$=0,00), 0,15 і 0,14 ($\chi2$=0,07) та 0,00 і 0,01 ($\chi2$=0,44) відповідно, без статистично значущих відмінностей (p=0,45). У контрольній групі частоти становили: 0,83 і 0,83 ($\chi2$=0,01), 0,18 і 0,16 ($\chi2$=0,12) та 0,00 і 0,10 ($\chi2$=0,61), також без значущих відмінностей (p=0,37).

Обговорення. Отримані результати свідчать про те, що поліморфізм rs5918 в гені ITGB3 не є основною мутацією, що сприяє розвитку гіперпластичних захворювань матки та молочних залоз. Крім того, у підгрупі пацієнток з гіперпластичними процесами матки не було виявлено зв'язку між цим поліморфізмом і супутньою патологією молочних залоз. Однак серед пацієнток, які мали аномальні маткові кровотечі, гетерозиготний генотип T/C був значно поширенішим.

Висновок. Окремий генетичний поліморфізм може мати незначний вплив на складні фізіологічні системи, проте сукупний ефект змін у декількох генах може значно порушити системний гомеостаз та спричинити патологічні стани. Отже, дослідження генетичної схильності до багатофакторних захворювань вимагає оцінки полігенних моделей або аналізу множинних поліморфізмів у відповідних генних шляхах.

Ключові слова: поліморфізм; гіперпластичні процеси матки; молочна залоза.

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