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Program for Predicting the Development of Benign Breast Diseases in Women with Hyperplastic Processes of the Uterus

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Abstract The study included the results of 82 patients with uterine hyperplastic processes (HPPU), who underwent a molecular genetic examination to determine the frequency of distribution of alleles and genotypes of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) in patients with HPPU, patients with HPPU and BMD, and conditionally -healthy female donors. Currently, an important direction of modern research in the field of preventive medicine is to determine the risk of developing pathology based on the search for significant molecular genetic predictors, and this method also makes it possible to determine the predisposition to hyperplastic processes of the uterus and mammary glands, their relapses and the development of neoplasia.

Keywords Polymorphism gene, Uterine hyperplastic processes

1. Introduction

In recent years, the incidence of benign breast dysplasia (BMD) in patients with gynecological pathology has increased worldwide. Hyperplastic processes of the uterus (HPPU) and mammary glands are one of the most common diseases in gynecological clinics and in our Republic.

According to the literature, HPPU can be detected in women aged 20-30, and sometimes even earlier. However, after 40 years, the risk of HPPU increases to 76-80%, and the disease continues to be a fairly common pathology in women during the perimenopause period.

GST genetic polymorphism is the main reason for many neurological dysfunctions. GST has over expressed in epileptic brain and pi (π) GST has used to predict stroke; mu (μ) and pi (π) GST are over expressed in Alzheimer's disease (AD).

HPPU is often the only pathology of the reproductive system, but it is often accompanied by hyperplastic processes of the mammary glands, which is explained by the same type of neuroendocrine changes in the hypothalamic-pituitary -ovarian and adrenal systems. Research conducted in recent years indicates a common pathogenesis of mammary gland pathology and dyshormonal diseases of the genital organs. According to G.M. Savelyeva, the development of uterine fibroids and mastopathy occurs simultaneously and the probability of a combination of these processes is 76-87%. According to some authors, the most severe forms of BMD are formed in women with uterine fibroids, adenomyosis, and hyperplastic processes of the endometrium. Other researchers suggest considering the priority of damage to the mammary glands as a marker of developing unified disorders in the reproductive system.

The concept of the multifactorial nature of hyperplastic diseases of the female reproductive system that has emerged in recent years suggests a special involvement of endocrine, immunological, hormonal, environmental, and genetic factors, the relative role of which is different in the genesis of each disease.

Despite a large number of studies on the condition of the mammary glands in terms of gynecological practice, many issues related to the principles of treatment and management of patients with combined hyperplasia of two hormone-dependent structures, methods for preventing the development of cancer and severe forms of mastopathy in patients with endometrial hyperplastic processes during perimenopause have not been sufficiently covered.

Research objective: To optimize the management of women with uterine hyperplastic processes by determining the polymorphism of the GSTP1 gene.

GSTP1 encodes an enzyme involved in Phase II drug metabolism that catalyzes the conjugation of glutathione to xenobiotics, leading to their excretion. [3]

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2. Research Materials and Methods

To analyze the distribution of allele and genotype frequencies of the rs1138272 polymorphisms in the GSTP1 gene (Ile/Val) in the study groups, their distribution by the studied polymorphic loci was checked for compliance with the RHC using Fisher's exact test in a sample group of 80 conditionally healthy female donors (control group) and 82 patients with HPPU (Group I - patients with HPPU (n=32) and Group II - patients with HPPU who had BMD (n=50)). Our analysis of the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) in the group of conditionally healthy donors (control) allowed us to establish the following facts: the frequency of the Ile allele was 81.2%, and the Val allele - 18.7% of the case. At the same time, carriage of the homozygous genotype Ile/Ile was determined in 66.2% (n=53), heterozygous genotype (Ile/Val) in 30.0% (n=24), and homozygous Val/Val in 3.7% (n=3) of cases (Table 1).

Next, we studied the distribution features of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) in the main group of patients with HPPU, which were characterized by the fact that the frequency of the Ile allele was 64.6% (n=106), and the Val allele was 35.4% (n=58). Along with this, in the studied group of patients, the frequency of carriage of the homozygous genotype Ile/Ile was 45.1% (n=37), the heterozygous genotype Ile/Val - 39.0% (n=32), and the homozygous mutant genotype Val/Val - 15.8% (n=13). In addition, we conducted a comparative analysis of the frequencies of alleles and genotypes in the context of groups of patients with HPPU. In particular, in group I of patients with only HPPU, the frequency of carriage of the Ile allele was 81.2% (n=52), and the Val allele – 18.7% (n=12), while carriage of the homozygous Ile/Ile genotype was detected in 68.7% (n=22), the heterozygous Ile/Val genotype in 25.0% (n=8) and the homozygous Val/Val genotype in 6.2% (n=2) of cases. Whereas in group II of patients with HPPU and BMD, the Ile allele was recorded in 54.0% (n=54), and the Val allele in 46.0% (n=46) of cases. The carriage of the homozygous genotype Ile/Ile was determined in 30.0% (n=15), the heterozygous genotype Ile/Val in 48.0% (n=24) and the homozygous mutant genotype Val/Val in 22% (n=11) of cases.

The results of assessing the distribution of allele and genotype frequencies of the rs1138272 polymorphism [5] in the GSTP1 gene (Ile/Val) show that in the main group of patients with HPPU, the proportion of Ile and Val alleles had a significant difference from the indicators in the group of conditionally healthy donors (control) ($\chi2$=11.3; p=0.01; OR=2.4; 95% CI: 0.68-2.32). A similar pattern was also observed with respect to the distribution of genotypes, i.e. there was a significant difference in the Ile/Ile genotype ($\chi2$=7.3; p=0.01; OR=0.4; 95% CI: 0.37-1.24), and in the Ile/Val genotype there was a similar pattern to the control group ($\chi2$=1.5; p=0.3; OR=1.5; 95% CI: 0.72-2.36). The result of assessing the occurrence of the mutant Val/Val genotype had a comparative difference between the main groups and the control group ($\chi2$=6.7; p=0.01; OR=4.8; 95% CI: 2.39-7.48). These data indicate a significant difference in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between the main group of patients with hyperplastic processes of the uterus and mammary glands and conditionally healthy donors (Table 2).

Table 1. Distribution frequency of alleles and genotypes of polymorphism rs1138272 in the GSTP1 gene (Ile/Val) in a group of conditionally healthy donors and in patients with hyperplastic processes

Group	n	Allele frequency				Genotype frequency distribution					
		Ile		Val		Ile/ Ile		Ile/Val		Val / Val	
		n	%	n	%	n	%	n	%	n	%
The main group of patients	82	106	64,6	58	35,4	37	45,1	32	39,0	13	15,8
I - group of patients with HPPU	32	52	81,2	12	18,7	22	68,7	8	25,0	2	6,2
II - group of patients with HPPU and BMD	50	54	54,0	46	46,0	15	30,0	24	48,0	11	22,0
Control group	80	130	81,2	30	18,7	53	66,2	24	30,0	3	3,7

Table 2. Analysis of differences in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between the main group of patients and the control group

Alleles and genotypes	Main group n=82		Control group n=80		χ^2	P	OR	95% CI
	n	%	n	%				
Ile	106	64,6	130	81,3	11,3	0,01	2,4	0.68-2,32
Val	58	35,4	30	18,8				
Ile/ Ile	37	45,1	53	66,3	7,3	0.01	0,4	0.37-1,24
Ile/Val	32	39,0	24	30.0	1,5	0.3	1.5	0.72-2,36
Val / Val	13	15,9	3	3,8	6,7	0.01	4,8	2,39-7,48

Table 3. Analysis of differences in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between group I patients and the control group

Alleles and genotypes	I group n=32		Control group n=80		χ^2	P	OR	95% CI
	n	%	n	%				
Ile	52	81,3	130	81,3	0,0	0,99	1,0	0.0- 0,0
Val	12	18,8	30	18,8				
Ile/ Ile	22	68,8	53	66,3	0,1	0.8	1.1	0.3- 3.6
Ile/Val	8	25,0	24	30,0	0.3	0.6	0,8	0.22- 3,2
Val / Val	2	6,3	3	3,8	0.3	0.6	1,7	0.19-14.8

Table 4. Analysis of differences in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between group II patients and the control group

Alleles and genotypes	II group n=50		Control group n=80		χ^2	P	OR	95% CI
	n	%	n	%				
Ile	54	54,0	130	81,3	22,1	0.01	3,7	0.85- 2.67
Val	46	46,0	30	18,8				
Ile/ Ile	15	30,0	53	66,3	16,2	0.01	0.2	0.17-1.2
Ile/Val	24	48,0	24	30,0	14,3	0,05	2,2	0,7- 3,68
Val / Val	11	22,0	3	3,8	10,7	0.01	7,2	2,82-12,2

Table 5. Analysis of differences in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between groups I and II of patients

Alleles and genotypes	I group n=32		II group n=50		χ^2	P	OR	95% CI
	n	%	n	%				
Ile	52	81,3	54	54,0	12,7	0.01	3,7	0.52-4,33
Val	12	18,8	46	46,6				
Ile/ Ile	22	68,8	15	30,0	11,8	0,01	5.1	0.7- 7,54
Ile/Val	8	25,0	24	48,0	4,3	0.05	0,4	0.14- 1,92
Val / Val	2	6,3	11	22,0	3,6	0.1	0.2	0.02- 3,65

The further assessment of the distribution of allele and genotype frequencies of the studied genetic polymorphism in groups I and II of patients with HPPU also allowed us to establish the absence of differences in relation to such indicators in the control group: group I frequency of Ile and Val alleles ($\chi2$=0.0; p=0.99; OR=1.0; 95% CI: 0.0-0.0), frequency of Ile/Ile genotypes ($\chi2$=0.1; p=0.8; OR=1.1; 95% CI: 0.3-3.6), Ile/Val ($\chi2$=0.3; p=0.6; OR=0.8; 95% CI: 0.22-3.2) and Val/Val ($\chi2$=0.3; p=0.6; OR=1.7; 95% CI: 0.19-14.8) (Table 3).

When studying the differences in the distribution of allele and genotype frequencies of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) in group II of patients and the control group, significant differences were found in both alleles and genotypes. Thus, the frequency of Ile and Val alleles ($\chi2$=22.1; p=0.01; OR=3.7; 95% CI: 0.85-2.67), the frequency of Ile/Ile genotypes ($\chi2$=16.2; p=0.01; OR=0.2; 95% CI: 0.17-1.2), Ile/Val ($\chi2$=4.3; p=0.05; OR=1.6; 95% CI: 0.7-3.68) and Val/Val ($\chi2$=10.7; p=0.01; OR=7.2; 95% CI: 2.82-12.22) (Table 4).

Next, we assessed the results in the distribution of allele and genotype frequencies between the main groups of patients with HPPU. In the results, we established significant differences in the distribution of both the Ile and Val alleles ($\chi2$=12.7; p=0.01; OR=3.7; 95% CI: 0.52-4.33) and the Ile/Ile genotypes ($\chi2$=11.8; p=0.01; OR=5.1; 95% CI: 0.7-7.54), Ile/Val ($\chi2$=4.3; p=0.05; OR=0.4; 95% CI: 0.14-1.92), and no differences were observed in the distribution of the mutant genotype Val/Val ($\chi2$=3.6; p=0.1; OR=0.2; 95% CI: 0.02-3.65) (Table 5).

3. Conclusions

Thus, the obtained data indicate the presence of statistically significant differences in the distribution of the frequencies of the Ile and Val alleles of the mutant genotypes Ile/Ile and Val/Val of the rs1138272 polymorphism in the GSTP1 gene (Ile/Val) between the main group of patients with uterine hyperplastic processes and conditionally healthy donors, which in turn allows us to identify these alleles and genotypes as genetic factors predisposing to an increased risk of developing [4] uterine hyperplastic processes and

benign breast dysplasia in women during perimenopause. Statistically significant differences were established in comparison with the values in conditionally healthy donors. In particular, in the main group of patients, an increase in the frequency of the Val allele by almost two times and the homozygous genotype and Val/Val by 2.4 times were established due to their levels in the group of patients with HPPU and BMD. These facts prove the role of the Val allele and the heterozygous genotype Ile / Val polymorphism rs1138272 in the GSTP1 gene (Ile / Val) in the risk of developing hyperplastic processes of the uterus and especially the combination of this pathology with benign dysplasia of the mammary glands in women in menopause.

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