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Bioinformatic Analysis of the Liability to the Hyperplastic Processes of the Uterus.

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ABSTRACT

This paper presents the results of bioinformatic analysis of five molecular genetic markers of 947 women with uterine hyperplasia and 988 women of the control group. We found that the genetic variation *TT rs7759938* in women of the Central region of Russia is associated with an increased risk of hyperplastic processes of the uterus (OR=1.35), and the protective value has the combination as follows: *C rs7759938* with *C rs2252673* (OR=0.72), *C rs7759938* with *C rs4374421* and *C rs466639* (OR=0.68), *CT rs4374421* with *CT rs466639* (OR=0.77), *T rs7579411* with *T rs4374421* (OR=0.78).

Keywords: hyperplastic processes of uterus, genetic polymorphism, bioinformatics.

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INTRODUCTION

Benign proliferative diseases of the female reproductive system such as the uterine fibroid, genital endometriosis, endometrial hyperplastic processes, based on the pathologic hyperplastic processes of endo- and myometrium tissues, occupy a leading place in the structure of the common gynecological morbidity [1].

According to the literature, uterine fibroid occurs in 20-35% of women of reproductive age, and after 50 years its prevalence is up to 70% [2-4]. Adenomyosis is present in 19.5% of the female population of reproductive age [5].Endometriosis accounts for 15-50% of all gynecological diseases [6-8]. Hyperplastic processes of the uterus have a common pathogenesis and therefore often occur concomitantly. 27% of women with endometriosis have a concomitant uterine fibroid. In addition, upon the uterus hysterectomy this combined pathology occurs in 15 to 57% of tissue samples of women with fibroids [9].

Now it is known that polymorphisms of several genes are important in the formation of disposition to the development of hyperplastic processes of uterus. However, the results of studies on the role of candidate genes in the formation of hyperplastic processes of the uterus are controversial in different populations.

MATERIALS AND METHODS

We conducted the analysis of the results of observations in 1935 people: 947 women with uterine hyperplasia and 988 women of the control group. The samples of case and control groups included women of Russian nationality being natives of the Central Black Earth Region of the Russian Federation and having no family ties with each other. Clinical and instrumental examination of patients with hyperplastic processes of the uterus was performed by doctors of the gynecological department of the Perinatal Center of St. Joasaph Belgorod Regional Clinical Hospital. The control group included women without gynecological diseases.

All patients with hyperplastic processes of the uterus and individuals of control group underwent typing of five molecular genetic markers: *LIN28B g.105485647C>T (rs7759938), LHCGR c.606-2195C>T (rs7579411), LHCGR c.680+695C>T (rs4374421), INSR c.2267+90G>C (rs2252673), RXRG c.-130-837A>G (rs466639).*

As the material for the study we used 8-9 ml of venous blood taken from the cubital vein of a proband. A genomic DNA was isolated from peripheral blood by the method of standard phenol-chloroform extraction [10]. Analysis of the investigated loci was carried out by the method of polymerase chain reaction of DNA synthesis with the use of oligonucleotide primers and probes.

Analysis of the role of combination of genes under study in the formation of hyperplastic processes of the uterus was performed by APSampler operating Markov chain Monte Carlo, and Bayesian nonparametric statistics. In performing multiple comparisons we used the Bonferroni correction (p_{cor}) in order to minimize the errors of the first kind [11].

RESULTS

We examined 947 women with uterine hyperplasia and 988 women of the control group. The main characteristics of the study groups are shown in Table 1. The control group is fully comparable to the sample of patients with hyperplastic processes of the uterus by age, ethnicity, place of birth and height-for-weight characteristics (p>0.05).

Table 1: Characteristics of the subjects from the case and control groups.

Characteristics	Cases	Controls
Total	988	947
Age, yrs	36.05±11.06*	35.2±7.5
Weight, kg	64.8±1.9*	62.4±2.8
Height, cm	164.8±4.1*	167.5±3.7

Note: *p>0.05

Study of the frequency of alleles in the investigated polymorphic markers of genes showed (Table 2) that the empirical distribution of genotypes corresponds to theoretically expected distribution at Hardy-Weinberg equilibrium (p> 0.05) for all studied loci in patients with hyperplastic processes of the uterus and in the control group.

Table 2: Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				χ^2	p
rs7759938	Case	C	55.28	0.89	>0.05
	Control	C	54.43	0.97	>0.05
rs7579411	Case	C	28.35	0.40	>0.05
	Control	C	30.10	0.32	>0.05
rs4374421	Case	C	31.01	0.35	>0.05
	Control	C	31.49	0.43	>0.05
rs2252673	Case	C	79.49	0.40	>0.05
	Control	C	79.47	0.17	>0.05
rs466639	Case	T	11.08	0.19	>0.05
	Control	T	12.36	0.44	>0.05

Notes: MAF, minor allele frequency; Hardy – Weinberg equilibrium. P values were calculated using the χ2 test.

Using bioinformatic analysis we identified a genetic variation associated with an increased risk of hyperplastic processes of the uterus: *TT rs7759938* (OR=1.35), and the following combinations have a protective value: *C rs7759938* with *C rs2252673* (OR=0.72), *C rs7759938* with *C rs4374421* with *C rs466639* (OR=0.68), *CT rs4374421* with *CT rs466639* (OR=0.77), *T rs7579411* with *T rs4374421* (OR=0.78) (Table 3).

Table 3: Concentration combinations of alleles/genotypes of genes considered in patients with hyperplastic processes of the uterus and the control group

SNP 1	SNP 2	SNP 3	Carriage		Fisher's p-value (Bonferroni correction, p_{cor})	Odds ratio (95% CI)
			Case	Control		
TT rs7759938			55.61	48.19	0.0007 (0.002)	1.35 (1.12-1.61)
C rs7759938	C rs2252673		41.83	49.95	0.0003 (0.0012)	0.72 (0.60-0.87)
C rs7759938	C rs4374421	C rs466639	20.81	27.78	0.0004 (0.003)	0.68 (0.55-0.85)
T rs7579411	T rs4374421		54.44	60.55	0.005 (0.03)	0.78 (0.64-0.94)
CT rs4374421	CT rs466639		37.75	44.02	0.004 (0.02)	0.77 (0.64-0.93)

DISCUSSION

According to our findings, a genetic variant *TT rs7759938* is a risk factor for hyperplastic processes of the uterus (OR=1.35). Pathogenic significance of *LIN28B rs7759938* in the formation of hyperplastic processes of the uterus identified in our study is consistent with literature data on its medical and biological effects in the body. Thus, *LIN28B* plays a key role in processes such as proliferation, differentiation, embryogenesis, and skeletal myogenesis, and is associated with insulin sensitivity [12, 13]. These pathogenetic mechanisms are important in the formation of hyperplastic processes of the uterus.

According to the literature, the *T LIN28B* allele is associated with menarche age (p=0.019) [14]. Large number of studies determined the involvement of *LIN28B* gene into the formation of ovarian cancer, prostate cancer, and colon cancer. It should be noted that overexpression of LIN28B is correlated with decreased patient survival rate and increased probability of metastasis growth [15].

SUMMARY

Based on the results of our study we may conclude that the *TT LIN28B* genotype is a risk factor for hyperplastic processes of the uterus (OR=1.35) in women of the Central region of Russia, while the following combinations serve as the protective factors of formation of hyperplastic processes of the uterus: *C rs7759938* with *C rs2252673* (OR=0.72), *C rs7759938* with *C rs4374421* and *C rs466639* (OR=0.68), *CT rs4374421* with *CT rs466639* (OR=0.77), *T rs7579411* with *T rs4374421* (OR=0.78).

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