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Gene Polymorphism And Endometrium Hyperplastic Processes.

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ABSTRACT

Hyperplastic processes of the endometrium are a chronic progressive disease characterized by high prevalence among women of older age groups. The objective of the study was the bioinformatical study of the involvement of candidate genes in the formation of endometrium hyperplastic processes. As a result of the study, 3 molecular-genetic markers were genotyped in 520 female patients with endometrium hyperplastic processes and 981 control women. It was found that among women from the Central region of Russia, the combination of molecular genetic markers G rs1398217, G rs887912 and G rs2090409 (OR=1.32) is a risk factor for the development of endometrium hyperplastic processes.

Keywords: endometrium hyperplastic processes, genetic polymorphism.

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INTRODUCTION

Hyperplastic processes of the endometrium are a chronic progressive disease, accompanied by pathological diffuse or focal proliferation of the glandular and stromal component of the uterine mucosa [Daya D., 2014]. In recent years, there has been an increase in endometrial disease among women of all age groups [Chandra V. et al., 2016]. The share of this pathology among gynecological diseases accounts for 10 to 50%, where the percentage of transformation into endometrial cancer is 5 to 10%. [Boyraz G. et al., 2016]. About 40% of young women with hyperplastic processes of the endometrium undergo surgical treatment, which often leads to a loss of reproductive function [Kadirogullari P. et al., 2015].

One of its symptoms in women of reproductive age is infertility. Most often, women suffer from acyclic bleeding. Asymptomatic course of endometrium hyperplastic processes can be observed in 10% of menstruating patients and in 40% of postmenopausal women [Orbo A. et al., 2016].

Now it is known that polymorphisms of several genes are important in the formation of disposition to the development of hyperplastic diseases of uterus [O'Hara A.J. 2012; Krivoshei, I.V. et al., 2015; Ponomarenko I.V. et al., 2016; Ponomarenko, I.V. et al., 2016 a]. However, the results of studies on the role of candidate genes in the formation of hyperplastic processes of the endometrium are controversial in different populations.

The objective of this research was to study the involvement of combinations of candidate genes in the formation of endometrium hyperplastic processes.

MATERIALS AND METHODS

We conducted the analysis of the results of observations in 1501 people: 520 women with endometrium hyperplasia and 981 control women. The samples of case and control groups included women of Russian nationality being natives of the Central region of the Russian Federation and having no family ties with each other. Clinical and instrumental examination of patients with hyperplastic processes of the endometrium 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 endometrium and individuals of control group underwent typing of five molecular genetic markers: rs1398217 *FUSSEL18/SKOR2*, rs2090409 *TMEM38B*, rs887912 *FLJ30838.* The choice of these polymorphic markers for the study is due to their significant regulatory and expression potential (HaploReg (v.4.1.) (http://compbio.mit.edu/HaploReg))

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 phenol-chloroform extraction (Mathew C.G., 1985). 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.

Statistical processing of data was carried out using STATISTICA forWindows 6.0 and MicrosoftExcel 2007 software packages. To analyze the compliance of the observed distribution of genotypes with the expected one, based on Hardy-Weinberg equilibrium, we used χ^2 test.

The role of combinations of genetic polymorphisms in the onset of endometrial hyperplasia was analyzed using APSampler [http://sources.redhat.com/cygwin/], operating Markov chain Monte Carlo, and Bayesian nonparametric statistics [Favorov A.V. et al., 2005].

RESULTS AND DISCUSSION

We examined 520 female patients with endometrial hyperplasia and 981 women of the control group. The main characteristics of the study and control groups are shown in Table 1. The control group is fully comparable to the sample of patients by age, ethnicity, and place of birth.

The analysis of the distribution of studied polymorphic markers of candidate genes showed that for all the studied loci in the group of patients with endometrium hyperplastic processes, as well as in the control

sample, the empirical distribution of genotypes corresponds to the theoretically expected one at Hardy-Weinberg equilibrium (p>0.05).

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

Characteristics	Cases	Controls
Total	520	981
Age, yrs	41.78±10.04	40.73±8.60
Height, cm	1.66±0.06	1.65±0.06
Weight, kg	73.67±14.66	72.64±13.54
IMB	26.94±5.56	26.78±4.67

A comparative analysis of the frequency distribution of alleles and genotypes of polymorphic markers showed no statistically significant differences between the patients with endometrial hyperplasia and those of the control group.

Bioinformatic approaches showed that a combination of the three genetic variants G rs1398217, G rs887912 and G rs2090409 in patients with endometrial hyperplasia (59.92%) occurs more often (1.13 times) than in the control group (53.14%, p=0.008, p_{perm}=0.0002). These data indicate a significant contribution of a combination of polymorphic variants of the genes rs1398217, rs887912 and rs2090409 in the formation of endometrial hyperplastic processes (OR=1.32, 95% CI 1.06-1.65).

Using HaploReg (v.4.1.) online service (http://compbio.mit.edu/HaploReg), the regulatory potential and the influence on the expression of genes of significant polymorphisms associated with hyperplastic endometrial processes were studied. The genetic polymorphism rs1398217 is localized in 49 kb from the 5' end of the *IER3IP1* gene. This locus is associated with the expression level of the *HDHD2* gene in skeletal muscle (p=3.04E-09) [Ardlie K.G. et al., 2015] and blood cells (p=3.48E-05) [Westra H.J. et al., 2013], and is also associated with the level of methylation of the 18th chromosomes (chr18: 42811583-42811633) in the cerebellum (p=1.13E-09) [Gibbs J.R. et al., 2013]. It is part of 18 DNA motifs, while the increased affinity of motifs is associated with the G allele (part of the "risky" combinations). This allele maximally increases the affinity of regulatory motifs: CAC-binding-protein (PWM=10.8), SP1_known1 (PWM=10.3), UF1H3BETA (PWM=12.0), ZNF219 (PWM=7.7). According to the results of the GWAS study, this locus is associated with the age at menarche (p=2E-13) [Elks C.E. et al., 2010].

The genetic polymorphism rs887912, located 12 kb from the 3' end of the *FLJ30838* gene has a high regulatory and expressive potential and marks histone proteins within the enhancers. The "risky" G allele of this locus increases the affinity of the DNA motif - Hoxa5_1 (PWM = -0.6), while its reference A allele is associated with increased affinity of the Znf143_known1 motif (PWM=1.0). This genetic polymorphism is associated with a body mass index (p=2E-22) [Speliotes E.K. et al., 2010] and anthropometric characteristics at pubertal age (p=1E-10) [Berndt S.I. et al., 2013].

A polymorphic locus rs2090409 is located 430 kb from the 3' end of the *TMEM38B* gene. This locus is associated with the level of expression in blood cells (p=2.2E-06) [Fehrmann R.S. et al., 2011]. Genetic polymorphism rs2090409 is a part of 3 DNA motifs - Foxp1, RREB-1 and YY1. It is established that the G allele (part of the "risky" combination) increases the affinity of the regulatory motif Foxp1 (PWM = -5.7). It should be noted that this locus is associated with the age at menarche (p=2E-9 and p=2E-33) [Elks C.E., et al., 2010; Perry J.R.B. et al., 2014], as well as anthropometric indices in the pubertal period (p=2E-6) [Cousminer D.L. et al., 2014].

SUMMARY

The materials obtained as a result of the bioinformatic analysis testify to the significant role of the studied genetic polymorphisms in the onset of endometrial hyperplasia. Thus, the combination of molecular genetic markers G rs1398217, G rs887912 and G rs2090409 is a risk factor for the development of endometrium hyperplastic processes in women from the Central region of Russia (OR=1.32).

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