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Genetic Variations of Interleukins are Associated with Hysteromyoma Developing.

Oksana Borisovna Altuchova*, Natalia Aleksandrovna Demakova, Sergey Petrovich Pachomov, and Irina Vitalevna Batlutskaya.

Belgorod State National Research University, 85, Pobedy St., Belgorod, 308015, Russia.

ABSTRACT

The article covers the data of comparison study of polymorphic variants frequency of interleukins genes in patients with hysteromyoma and women in the control group. There were determined associations of genetic polymorphisms *IL-1α c.-949 C>T (rs1800587)*, *IL-5 c.-746 T>C (rs2069812)* and their combinations with hysteromyoma developing in the women of Russia Central Region.

Keywords: hysteromyoma, interleukins, polymorphisms.

Corresponding author

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INTRODUCTION

Hysteromyoma is a benign, well determined capsulated tumor, which origin are smooth muscle cells of uterine cervix and uterine body. Hysteromyoma takes the first place among the genitalia benign tumors; at this, one in ten patients suffers from the hysteromyoma [1]. Contemporary ideas about etiology of this pathology process are based on achievements of endocrinology, immunology, molecular biology, and genetics.

In recent times, there are more and more data testifying that polymorphisms of some genes has a great importance in formation of underlying risk for hysteromyoma developing. According to literature data, more than 100 genes can take part in hysteromyoma formation, most of these genes participate in regulation of cell development, differentiation, proliferation, and inflammatory process [2]. Among the genes-candidates participating in regulation of immunological and inflammatory processes in myometrium, interleukins genes are of great importance [3-5]. In this regard, this work studies the role of genetic polymorphisms of interleukins (*IL-6 c.-237 C>G (rs1800795), IL-1β c.-598 T>C (rs16944), IL-1α c.-949 C>T (rs1800587), IL-4 c.-589 C>T (rs2243250), IL-10 c.-627 A>C (rs180082), IL-5 c. -746 T>C (rs2069812)* in formation of hysteromyoma in the women of Russia Central Region.

MATERIALS AND METHODS

Investigation of associations of polymorphic markers of interleukins genes under study was pursued at sampling of 617 cases, among them, 117 are with hysteromyoma, and 500 persons of control group. The sampling were women of Russian nationality coming from Russia Central Region and not being relatives. Clinic laboratory investigation was pursued based on gynecology department of perinatal center St. Joasaph Belgorod Regional Clinic Hospital. Patients with hysteromyoma were made an ultrasound investigation of pelvic organs, hysteroscopy with the following target biopsy of the lining of the uterus and scrape histologic examination; there were applied general and laboratory study methods.

All the patients with hysteromyoma and the control group samples had typing of six molecular and genetic markers: interleukin-6 *(IL-6 c.-237 C>G (rs1800795)),* interleukin-*1β (IL-1β c.-598 T>C (rs16944)),* interleukin-*1α (IL-1α c.-949 C>T (rs1800587)),* interleukin-4 (*IL-4 c.-589 C>T (rs2243250)),* interleukin-10 *(IL-10 c.-627 A>C (rs180082)),* interleukin-5 *(IL-5 c. -746 T>C (rs2069812)).*

As a material, one used black blood in volume of 8-9 ml taken from the median cubital vein of proband. Genomic DNA was extracted from peripheral blood by standard methods [6].

Molecular genetic estimation of all the locuses was performed by method of polymerase chain reaction of DNA synthesis using oligonucleotide primers and probes [7, 8, 9]. Genotyping of DNA markers is performed by method of TaqMan probes detection according to data of level value relative to fluorescence of each probe at «IQ5» amplificator with detecting system in real-time mode (*IL-4 c.-589 C>T (rs2243250), IL-6 c.-237 C>G (rs1800795))*. It was also used the method of analyses of restriction fragment length polymorphism (RFLP) of products of PCR-amplification of genome specific sectors using the corresponding restriction enzymes (*IL-1α c.-949 C>T (rs1800587), IL-1β c.-598 T>C (rs16944), IL-5 c.-746 T>C (rs2069812), IL-10 c.-627 A>C (rs180082*)).

To estimate the correspondence of genotype distribution under study to the expected one, and based on Hardy-Weinberg equilibrium, one used χ^2 test. Associations of alleles and genotypes of the studied DNA-markers with hysteromyoma formation were estinated with the contingency tables 2x2 analyses, taking into account χ2 test and Yates correction for regularity and odds ratio (OR) with 95% confidence intervals (CI).
Estimation of role of interleukins genetic variants combinations in contraction of hysteromyoma is performed using the software APSampler using Markov chains Monte Carlo technique and Bayesian distribution-free statistics. In order to minimize type I errors, Bonferroni correction (p_{cor}) and permutation test (p_{perm}) were used for multiple comparisons [10].

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RESULTS

After examination of 117 women with hysteromyoma and 500 women from the control group, it was determined, that the control group is completely commeasurable with sampling of cases with hysteromyoma by gender, age, nationality and place of birth, and by height and weight (p>0.05).

Examination of alleles concentration of genes polymorphic markers under study showed that for all the examined locuses in the group of patients with hysteromonia and in population sampling, empiric genotype distribution corresponded to the expected one at Hardy-Weinberg equilibrium (p>0.05) (Table 1).

Table 1: Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				χ^2	p
IL-1α c.-949 C>T (rs1800587)	Case	*T*	33.33	2.67	>0.05
IL-1α c.-949 C>T (rs1800587)	Control	*T*	20.40	1.31	>0.05
IL-1β c.-598 T>C (rs16944)	Case	*T*	33.01	0.001	>0.05
IL-1β c.-598 T>C (rs16944)	Control	*T*	34.58	0.25	>0.05
IL-4 c.-589 C>T (rs2243250)	Case	*T*	17.12	0.25	>0.05
IL-4 c.-589 C>T (rs2243250)	Control	*T*	18.87	0.19	>0.05
IL-5 c.-746 T>C (rs2069812)	Case	*T*	25.60	0.77	>0.05
IL-5 c.-746 T>C (rs2069812)	Control	*T*	27.59	0.004	>0.05
IL-6 c.-237 C>G (rs1800795)	Case	*C*	41.75	0.68	>0.05
IL-6 c.-237 C>G (rs1800795)	Control	*C*	44.63	0.01	>0.05
IL-10 c.-627 A>C (rs180082)	Case	*A*	20.35	0.085	>0.05
IL-10 c.-627 A>C (rs180082)	Control	*A*	24.44	1.42	>0.05

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

Among the cases with hysteromyoma (14.71% and 33.33%, respectively), there were determined high genetic variants frequency *TT IL-1α* and *T IL-1α* in comparison with the control group (3.26%, χ^2=18.74, p=0.01, p_{cor}=0.003, OR=5.11, 95%CI 2.24-11.69 and 20.40%, χ^2=18.74, p=0.001, OR=1.95, 95%CI 1.37-2.76, respectively).

While using bio-informational approaches, is was determined that combination of two genetic variants *TT IL-1α* and *C IL-5* in the group of cases with hysteromyoma (14.47%) is much more often (6.8 times more) than in the control group (2.12%, p_{bonf}=0.02, p_{perm}=0.0002). These data testify about a great contribution of combination of polymorphicc genes variants *IL-1α* and *IL-5* to hysteromyoma formation (OR=7.78) (Table 2).

Table 2: Concentration combinations of alleles/genotypes of interleukins genes in patients with hysteromyoma and in the control group

SNP 1	SNP 2	Carriage		Fisher's p-value (Bonferroni correction, p_{cor}) Permutation test, p_{perm}	Odds ratio (95% CI)
		Case	Control		
TT IL-1α	*C IL-5*	14.47	2.12	0.0001 (0,02) 0.0002	7.78 (2.61-23.21)

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AFTERWARDS

The got data testify about great etiopathogenetic importance of genetic polymorphisms *-889 C/T* of interleukins 1α at hysteromyoma. At this, genotype *TT IL-1α* and allele *T IL-1α* are the hysteromyoma risk factors (OR=5.11 and OR=1.95, respectively). According to our obtained data, there was determined a "risk" combination of genetic variants *TT IL-1α* and *C IL-5* (OR= 7.78) related to hysteromyoma formation.

According to literature data, polymorphisms *IL-1α c.-949 C>T (rs1800587)* is in the gene coding sequence and can influence on protein expression level. Among the cases homozygous by allele *T IL-1A*, plasma levels *IL-1A* are increased in comparison to other genotypes carriers [11]. It is known that a series of tumor cells are able to reproduce *IL-1A*, in connection with it, realization of antitumor response is violated; this violation can lead to more severe disease.

CONCLUSIONS

Consequently, it was determined that genotype *TT IL-1α* and allele *T IL-1α* are the hysteromyoma risk factors (OR=5.11 и OR=1.95, respectively). Combination of genetic variant *TT IL-1α* with allele *C IL-5A* (OR=7.78) is associated with hysteromyoma developing.

REFERENCES

[1] Gornall AS, Naftalin NJ, Brown LJR and Konje JC. Int J Obstetr Gynaecol 2000;107(4): 573-575.
[2] Parker WH. Fert Steril 2007;88(2): 255-271.
[3] Sosna O, Kolesar L, Slavcev A, Skibova J, Fait T, Mara M, and Kuzel D. Folia Biol 2010;56(5):206-10.
[4] Taghizade-Mortezaee F, Hashemzadeh-Chaleshtori M, Kheiri S, Parvin N, Norbakhsh M, Etemadi S, and Mirj S. Zahedan J Res Med Sci 2012;14(7): 53-56.
[5] Khorasani MM, Salimi S, Hajizade A, Moossavi M, Tabatabai E, Yaghmaei M, and Mashhadi FF. Gene Cell Tissue 2014;1(1):5.
[6] Miller SA, Dykes DD, Polesky HF. Nucleic Acids Res 1988;16(3): 1215.
[7] Trevilatto PC, Scarel-Caminaga RM, De Brito RB, De Souza AP, and Line SR. J Clin Periodontol 2003;30(5): 438-442.
[8] Steinbrugger I, Haas A, Maier R, Renner W, Mayer M, Werner C, and Weger M. Mol Vision 2009;15: 609.
[9] Landi S, Moreno V, Gioia-Patricola L, Guino E, Navarro M, de Oca J, and Canzian F. Cancer Res 2003;63(13): 3560-3566.
[10] Favorov AV, Andreewski TV, Sudomoina MA, Favorova OO, Parmigiani G, and Ochs MF. Genetics 2005; 171(4): 2113-2121.
[11] Hutyrova B, Pantelidis P, Drabek J, Zurkova M, Kolek V, Lenhart K, and Petrek M. American J Respir Crit Care Med 2002;165(2): 148-151.