



Research Article

Epistatic interactions in formation of hysteromyoma

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ABSTRACT

Aim: The article highlights the bioinformatics analysis data of eight polymorphous loci among 569 patients with hysteromyoma and 981 women from the control group. **Material and Methods:** Investigation of associations of polymorphic markers genes under study was pursued at sampling of 1214 cases, among them, 227 are with hysteromyoma, and 987 persons of the control group. **Results:** It was found that the increased risk of hysteromyoma in women of Russia Central region is connected with the combination of the following molecular genetic markers: C rs4633 with C rs2288696 with 1398217 with G rs3756261 with G rs1079866 and T rs10441737 (odds ratio [OR] = 2.28), and the protective effect has the combination of alleles T rs466639 with C rs1398217 and A rs11031010 (OR = 0.32). **Conclusion:** Thus, in the process of the research, it was found that the risk of hysteromyoma in women of the Central Black Soil Region of the Russian Federation, is raised by the combination of the molecular.

KEY WORDS: Bioinformatics, Genetic polymorphism, Hysteromyoma

INTRODUCTION

Hysteromyoma is benign monoclonal tumors of the uterine smooth muscle cells and consists of large amounts of extracellular matrix that contain collagen, fibronectin, and proteoglycan.^[1] The prevalence of hysteromyoma varies between 5% and 65% depending on age, ethnicity, geographical region, and quality of imaging techniques.^[2]

The majority of hysteromyomas are asymptomatic, however up to 20% cause menorrhagia, pelvic pain, and genitourinary symptoms.^[3,4] Hysteromyomas are associated with 10% of infertility cases and are a sole cause of infertility in 1-3% of patients.^[5] They can occur as single or multiple focal fibroids or can be diffuse. Hysteromyomas are most often diagnosed in the perimenopausal years. The incidence of hysteromyoma declines after menopause.

The mechanism for the development of hysteromyoma is poorly understood. Both genetic factors such as mutations and environmental factors have been implicated in the development of hysteromyoma.^[6,7] According to literature data,

more than 100 genes can take part in hysteromyoma formation.^[8,9]

MATERIALS AND METHODS

Investigation of associations of polymorphic markers genes under study was pursued at sampling of 1214 cases, among them, 227 are with hysteromyoma, and 987 persons of the control group. The sampling was 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 eight molecular and genetic markers: *COMT* c.186C>T (rs4633), *FGFR1* c.359-272C>T (rs2288696), *FUSSEL18/SKOR2* c.2917+4592C>G (rs1398217), *EGF* c.-2186T>C (rs3756261), *INHBA* g.41470093C>G (rs1079866), *ZNF483* c.721+4952C>T (rs10441737), *RXRG* c.-130-837T>C (rs466639), and *FSHB* g.30240178C>A (rs11031010).

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Molecular genetic estimation of all the locuses was performed by the method of polymerase chain reaction of DNA synthesis using oligonucleotide primers and probes.^[10] Genotyping of DNA markers is performed by the method of TaqMan probes detection according to data of level value relative to the fluorescence of each probe at “IQ5” amplifcator with detecting system in real-time mode.

To estimate the correspondence of genotype distribution understudy to the expected one, and based on Hardy–Weinberg equilibrium, one used χ^2 test. Estimation of the role of genetic variants combinations in contraction of hysteromyoma is performed using the software APSampler using Markov chains Monte Carlo technique and Bayesian distribution-free statistics.^[11]

RESULTS AND DISCUSSION

After examination of 569 women with hysteromyoma and 981 women from the control group, it was determined, that the control group is completely commensurable with sampling of cases with hysteromyoma by gender, age, nationality, and place of birth, and by height and weight ($P > 0.05$). Main characteristics of the studied groups are given in Table 1.

Examination of alleles concentration of genes polymorphic markers under study showed that for all the examined locuses in the group of patients with hysteronomia and in population sampling, empiric genotype distribution corresponded to the expected one at Hardy–Weinberg equilibrium ($P > 0.05$) (Table 2).

While using bioinformational approaches, it was determined that the combination of six genetic variants C *COMT* (rs4633) with C *FGFR1* (rs2288696) with G *FUSSEL18/SKOR2* (rs1398217) with G *EGF* (rs3756261) with G *INHBA* (rs1079866) and T *ZNF483* (rs10441737) in the group of cases with hysteromyoma (8.56%) is much more often (2.2 times more) than in the control group (3.94%, $P = 0.0003$). These data testify about a great contribution of the combination of polymorphic genes variants rs4633 with rs2288696 with rs1398217 with rs3756261 with rs1079866 and rs10441737to hysteromyoma formation (odds ratio [OR]= 2.28).

Table 1: Characteristics of the individuals from the case and control groups

Characteristics	Cases	Controls
Total	569	981
Age, years	41.20±9.05	43.1±7.7
Weight, kg	61.3±1.9	64.4±1.6
Height, cm	162.8±5.1	164.4±4.6

The catechol-O-methyltransferase (*COMT*) catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines including the neurotransmitters dopamine, epinephrine, and norepinephrine. This O-methylation results in one of the major degradative pathways of the catecholamine transmitters. In addition to its role in the metabolism of endogenous substances, COMT is important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease. COMT is found in two forms in tissues, a soluble form (S-COMT) and a membrane-bound form (MB-COMT). The differences between S-COMT and MB-COMT reside within the N-termini. Several transcript variants are formed through the use of alternative translation initiation sites and promoters.^[12]

The protein encoded by this gene is a member of the fibroblast growth factor receptor (FGFR) family, where amino acid sequence is highly conserved between members and throughout evolution. FGFR family members differ from one another in their ligand affinities and tissue distribution. A full-length representative protein consists of an extracellular region, composed of three immunoglobulin-like domains, a single hydrophobic membrane-spanning segment and a cytoplasmic tyrosine kinase domain. The extracellular portion of the protein interacts with fibroblast growth factors, setting in motion a cascade of downstream signals, ultimately influencing mitogenesis, and differentiation. This particular family member binds both acidic and basic fibroblast growth factors and is involved in limb induction. Mutations in this gene have been associated with Pfeiffer syndrome, Jackson-Weiss syndrome, Antley-Bixler syndrome, osteoglophonic dysplasia, and autosomal dominant Kallmann syndrome 2. Chromosomal aberrations involving this gene are associated with stem cell myeloproliferative disorder and stem cell leukemia lymphoma syndrome. Alternatively, spliced variants which encode different protein isoforms have been described; however, not all variants have been fully characterized.^[13]

SKI family transcriptional corepressor 2 (*FUSSEL18/SKOR2*) exhibits transcriptional repressor activity.^[14]

Epidermal growth factor (EGF) encodes a member of the EGF superfamily. The encoded preproprotein is proteolytically processed to generate the 53 amino acid EGF peptide. This protein acts a potent mitogenic factor that plays an important role in the growth, proliferation, and differentiation of numerous cell types. This protein acts by binding with high affinity to the cell surface receptor, EGF receptor. Defects in this gene are the cause of hypomagnesemia type 4. Dysregulation of this gene has been associated with the growth and progression of certain cancers. Alternative splicing results in multiple transcript

Table 2: Summary information about the studied polymorphisms

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				χ^2	<i>P</i>
<i>COMT</i> c. 186C>T (rs4633)	Case	T	52.12	0.41	>0.05
<i>COMT</i> c. 186C>T (rs4633)	Control	T	54.21	1.15	>0.05
<i>FGFR1</i> c. 359-272C>T (rs2288696)	Case	T	27.27	0.52	>0.05
<i>FGFR1</i> c. 359-272C>T (rs2288696)	Control	T	24.58	1.21	>0.05
<i>FUSSEL18/SKOR2</i> c.2917+4592C>G (rs1398217)	Case	G	65.25	0.001	>0.05
<i>FUSSEL18/SKOR2</i> c.2917+4592C>G (rs1398217)	Control	G	67.12	1.74	>0.05
<i>EGF</i> c.-2186T>C (rs3756261)	Case	C	27.865	0.30	>0.05
<i>EGF</i> c.-2186T>C (rs3756261)	Control	C	29.35	0.84	>0.05
<i>INHBA</i> g. 41470093C>G (rs1079866)	Case	G	9.74	0.31	>0.05
<i>INHBA</i> g. 41470093C>G (rs1079866)	Control	G	7.69	0.94	>0.05
<i>ZNF483</i> c. 721+4952C>T (rs10441737)	Case	C	53.23	0.54	>0.05
<i>ZNF483</i> c. 721+4952C>T (rs10441737)	Control	C	55.12	1.08	>0.05
<i>RXRG</i> c.-130-837T>C (rs466639)	Case	T	26.16	0.52	>0.05
<i>RXRG</i> c.-130-837T>C (rs466639)	Control	T	24.25	1.25	>0.05
<i>FSHB</i> g. 30240178C>A (rs11031010)	Case	A	6.84	0.34	>0.05
<i>FSHB</i> g. 30240178C>A (rs11031010)	Control	A	8.68	0.74	>0.05

MAF: Minor allele frequency, HWE: Hardy-Weinberg equilibrium. P values were calculated using the χ^2 test

variants at least one of which encodes a preproprotein that is proteolytically processed.^[15]

The inhibin beta-A (*INHBA*) subunit joins the alpha-subunit to form a pituitary follicle-stimulating hormone (FSH) secretion inhibitor. Inhibin has been shown to regulate gonadal stromal cell proliferation negatively and to have tumor-suppressor activity. In addition, serum levels of inhibin have been shown to reflect the size of granulosa cell tumors and can therefore be used as a marker for primary as well as recurrent disease. Because expression in gonadal and various extragonadal tissues may vary several folds in a tissue-specific fashion, it is proposed that inhibin may be both a growth/differentiation factor and a hormone. Furthermore, the beta-A subunit forms a homodimer, activin A, and also joins with a beta-B subunit to form a heterodimer, activin AB, both of which stimulate FSH secretion.^[14]

Zinc finger protein 483 (*ZNF483*) may be involved in transcriptional regulation.^[16] Among patients with hysteroscopy, it was recorded the lowest frequency of combination alleles T *RXRG* (rs466639) with

C *FUSSEL18/SKOR2* (rs1398217) and A *FSHB* (rs11031010) (1.82%) compared to the control group (5.41%, *P* = 0.0003, OR = 0.32).

Retinoid X receptor gamma (*RXRG*) encodes a member of the *RXRG* family of nuclear receptors which are involved in mediating the antiproliferative effects of retinoic acid (RA). This receptor forms dimers with the RA, thyroid hormone, and Vitamin D receptors increasing both DNA binding and transcriptional function on their respective response elements. This gene is expressed at significantly lower levels in nonsmall cell lung cancer cells. Alternatively, spliced transcript variants have been described.^[17]

FSH, beta polypeptide encodes the beta-subunit of FSH. In conjunction with luteinizing hormone, FSH induces egg and sperm production. The pituitary glycoprotein hormone family includes FSH, luteinizing hormone, chorionic gonadotropin, and thyroid-stimulating hormone. All of these glycoproteins consist of an identical alpha-subunit and a hormone-specific beta-subunit.^[13]

CONCLUSION

Thus, in the process of the research, it was found that the risk of hysteromyoma in women of the Central Black Soil Region of the Russian Federation, is raised by the combination of the following molecular genetic markers: C rs4633 with C rs2288696 with G rs1398217 with G rs3756261 with G rs1079866 and T rs10441737 (OR = 2.28), and the combination of alleles has protective properties: T rs466639 with C rs1398217 and A rs11031010 (OR = 0.32).

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