ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Analysis of Candidate Genes for Uterine Fibroids.

Sergey P. Pachomov, Irina V. Ponomarenko, Vladimir F. Kulikovskiy, Valentina S. Orlova, Evgeny N. Krikun, Inna N. Sorokina, Irina V. Batlutskaya, and Olga Y. Bushueva.

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

ABSTRACT

The article presents the results of the comparative analysis of frequencies of polymorphic variants of 5 genes among patients with uterine fibroid and control groups. It was found that among women in the Central region of Russia protective factor in the formation of uterine fibroids is a molecular-genetic marker of TS rs7753051 (OR=0.81).

Keywords: uterine fibroids, genetic polymorphism.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Uterine fibroids – the most common benign tumor in women in most countries [1 - 3]. In 30-35% of women uterine fibroids are diagnosed at reproductive age and in 1/3 of cases, is accompanied by such clinical manifestations as uterine bleeding, anemia, and pelvic pain [4]. Most young women with this disease remain fertile, with the exception of submucosal forms of the disease, but the relationship between this tumor and infertility increases with age. For 40 years, when infertility and uterine fibroids reach a "peak" (60 and 40%, respectively), their combination could increase to 24% [5, 6]. In addition, the presence of uterine fibroids can cause complications with pregnancy and childbirth [7]. Uterine fibroids are the leading cause of hysterectomy in many countries of the world. In Russia, according to various reports, with uterine fibroids due to 50-70% cases of hysterectomy diseases of the uterus. This pathology is the cause of a significant reduction in the quality of life for the majority of the female population.

To the known risk factors for developing uterine fibroids include age, early menarche, fertility decline and lack of delivery that may be associated with more prolonged exposure to estrogen, and older age at first pregnancy, obesity, diabetes, hypertension, and adverse family history of uterine fibroids [8].

Despite the high prevalence, the exact pathophysiological mechanisms contributing to the development and growth of uterine fibroids are not completely clear.

MATERIALS AND METHODS

The analysis of the results of observations 1570 employees: 580 patients with uterine fibroid and 990 women in the control group was carried out. In the sample of patients and controls included women of Russian nationality who are native of the Central Black Mould Region of the Russian Federation and not consisting in relationship among themselves. Clinical-instrumental examination of patients with uterine fibroid was carried out by doctors of Gynecological Department of the Perinatal Center of the Belgorod Regional Clinical Hospital of Saint Joasaph. The control group included women without gynecological diseases.

All patients with uterine fibroid and individuals of the control group carried out the typing of five molecular genetic markers: IGF2R c.*1941T>C (rs7753051), EFR3B c.2421T>C (rs2164808), COMT c.186C>T (rs4633), INSR :c.2267+90G>C (rs2252673), UGT2B4 g.69488760C>T (rs2013573).

Venous blood in a volume of 8-9 ml taken from the cubital vein of the proband was as material for the study. The allocation of genomic DNA from the peripheral blood carried out by standard phenol-chloroform extraction [9]. Analysis of the investigated loci was performed by polymerase chain reaction of DNA synthesis using oligonucleotide primers and probes.

Statistical data processing was performed using software package "STATISTICA for Windows 6.0" and "Microsoft Excel 2007". The $\chi 2$ criterion with Yates correction for continuity were used for comparison of frequencies of alleles and genotypes between groups. The calculations were made in 2x2 contingency tables.

Association of alleles and genotypes of the studied DNA markers with the development of hypertension in individuals with positive family history was estimated using analysis of contingency tables 2x2 calculating the criterion c2 with Yates correction for continuity and odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

We studied 580 patients with uterine fibroid and 990 people in the control group. The main characteristics of the studied groups of patients with uterine fibroid and control are presented in table 1. The monitoring group are fully comparable with the sample of uterine fibroid at the age index, nationality and place of birth.

ISSN: 0975-8585

Table1. Characteristics of the subjects from the case and control groups.

Characteristics	Cases	Controls
Total	580	990
Age, yrs	36.09±8.06	39.3±10.03
Weight, kg	59.9±2.0	63.7±2.6
Height, cm	163.6±3.1	169.6±3.8

Study of the population genetic characteristics of the studied genetic markers revealed (table. 2) that for all the examined locus, among patients with essential hypertension and in control group, the observed distribution of genotypic variants corresponds to the theoretically anticipated equilibrium of Hardy-Weinberg ($p>0.05$).

Table 2. Summary information about the studied polymorphisms.

Polymorphism	Studied groups	Minor allele	MAF (%)	HWE	
				$\chi2$	p
IGF2R c.*1941T>C (rs7753051)	Case	C	11.19	1.21	>0.05
IGF2R c.*1941T>C (rs7753051)	Control	C	17.38	1.59	>0.05
EFR3B c.2421T>C (rs2164808)	Case	T	13.41	0.79	>0.05
EFR3B c.2421T>C (rs2164808)	Control	T	18.26	1.23	>0.05
COMT c.186C>T (rs4633),	Case	T	13.36	0.56	>0.05
COMT c.186C>T (rs4633),	Control	T	18.38	1.16	>0.05
INSR :c.2267+90G>C (rs2252673)	Case	C	17.23	0.25	>0.05
INSR :c.2267+90G>C (rs2252673)	Control	C	18.70	0.69	>0.05
UGT2B4 g.69488760C>T (rs2013573)	Case	T	17.97	1.28	>0.05
UGT2B4 g.69488760C>T (rs2013573)	Control	T	19.43	1.96	>0.05

Notes: MAF, minor allele frequency; Hardy – Weinberg equilibrium. P values were calculated using the $\chi2$ test. Locus rs7753051 received that patients with uterine fibroids have a lower concentration of genotype TC rs7753051 (of 40.31%) compared to the control group (45.56%, $\chi2=3.87$, $p=0.04$, OR=0.81, 95%Cl 0.65-0.98).

DISCUSSION

Insulin-like growth factor of 2 receptor (IGF2R), also known as the cation-independent mannose-6-phosphate (M6P) receptor is a transmembrane glycoprotein [10]. IGF2R is involved in various biological processes such as glucose homeostasis [11], the replication of HIV [12] and carcinogenesis [13]. According to the literature, IGF2R is a tumor suppressor [14]. Expression of wild-type M6P/IGF2R reduces tumor growth and the degree of invasion in squamous cell carcinoma [15].

It should be noted that IGF2R is implemented through the biological effect of insulin-like growth factor. According to the literature, insulin-like growth factor plays a key role in various cellular processes such as proliferation, differentiation, apoptosis, and participates in the maintenance of homeostasis [16]. Moreover, increased expression of insulin-like growth factor is observed in ovarian cancer, breast cancer, colon and correlates with reduced patient survival and resistance to therapy [17, 18].

CONCLUSION

Thus, the results allow us to conclude that among women in the central region of Russia the

protective factor in the formation of uterine fibroids is a molecular-genetic marker of TS rs7753051 (OR=0.81).

REFERENCES

[1] Taylor, D. K., Holthouser, K., Segars, J.H., 2014. Recent scientific advances in leiomyoma (uterine fibroids) research facilitates better understanding and management, J List, 4: 183.

[2] Churnosov, M.I., Altuchova, O.B., Demakova, N.A., Krivoshei, I.V., Evdokimov, V.I., Batlutskaya, I.V., Polonikov, A.V., 2014. Associations of Cytokines Genetic Variants with Myomatous Knots Sizes. Research Journal of Pharmaceutical, Biological and Chemical, 5(6): 1344-1347.

[3] Altuchova, O. B., Demakova, N. A., Pachomov, S. P., Batlutskaya, I. V., 2014. Genetic Variations of Interleukins are Associated with Hysteromyoma Developing. Research Journal of Pharmaceutical, Biological and Chemical, 5(5): 1065-1068.

[4] Tan, N., 2014. Women seeking second opinion for symptomatic uterine leiomyoma: role of comprehensive fibroid center. Journal of Ther Ultrasound, 2. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265989/ (accessed 15.04.2014).

[5] Segars, J. H., Parrott, E. C., Nagel, J. D., Guo, X. C., Birnbaum, L. S., Pinn, V. W., Dixon, D., 2014. Proceedings from the Third National Institutes of Health International Congress on Advances in Uterine Leiomyoma Research: comprehensive review, conference summary and future recommendations. Hum Reprod Update, 20(3): 309–333.

[6] Krivoshei, I.V., Altuchova, O.B., Golovchenko, O.V., Orlova, V.S., Polonikov A.V., Churnosov M.I., 2015. Genetic factors of hysteromyoma. Research Journal of Medical Sciences, 9(4):182-185.

[7] Jaslow C.R. Uterine Factors. Obstet Gynecol Clinics, 41(1): 57-86.

[8] Khan, A.T., Shehmar, M., Gupta, J.K., 2014. Uterine fibroids: current perspectives. Int J Womens Health, 6: 95–114.

[9] Miller, S. A., Dykes,D.D., Polesky,H.F. 1988. A simple salting out procedure for extracting DNA from human nucleated cells. Nucleic acids research, 16(3): 1215.

[10] Suh, H.-S., Cosenza-Nashat ,M, Choi, N., Zhao, M.-L., Li, J., Pollard, J.W, Jirtle, R. L., Goldstein, H., Lee, S.C., 2010. Insulin-Like Growth Factor 2 Receptor Is an IFNγ-Inducible Microglial Protein that Facilitates Intracellular HIV Replication Implications for HIV-Induced Neurocognitive Disorders Am J Pathol., 177(5): 2446–2458.

[11] Chanprasertyothin, S., Jongjaroenprasert, W., Ongphiphadhanakul B., 2015. The Association of Soluble IGF2R and IGF2R Gene Polymorphism with Type 2 Diabetes. J Diabetes Res. 2015: 2163-83. doi: 10.1155/2015/216383

[12] Suh, H.-S., Cosenza-Nashat, M., Choi, N., 2010. Insulin-like growth factor 2 receptor is an IFN*γ*-inducible microglial protein that facilitates intracellular HIV replication: implications for HIV-induced neurocognitive disorders. The American Journal of Pathology, 177(5):2446–2458.

[13] Martin-Kleiner, I., Gall Troselj, K., 2010. Mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R) in carcinogenesis. Cancer Letters, 289(1):11–22.

[14] Schiller, H.B., Szekeres, A., Binder, B.R., Stockinger, H., Leksa, V., 2009. Mannose 6-Phosphate/Insulin-like Growth Factor 2 Receptor Limits Cell Invasion by Controlling αVβ3 Integrin Expression and Proteolytic Processing of Urokinase-type Plasminogen Activator Receptor. Mol Biol Cell,1; 20(3): 745–756.

[15] Probst, O.C., Karayel, E., Schida, N., Nimmerfall, E., Hehenberger, E., Puxbaum, V., Mach, L., 2013. The mannose 6-phosphate-binding sites of M6P/IGF2R determine its capacity to suppress matrix invasion by squamous cell carcinoma cells. J. Biochem, 451(Pt 1): 91–99.

[16] Pollak, M., 2008. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer, 8:915–28.

[17] Tian, D., Mitchell, I., Kreeger, P.K., 2016. Quantitative analysis of insulin-like growth factor 2 receptor and insulin-like growth factor binding proteins to identify control mechanisms for insulin-like growth factor 1 receptor phosphorylation. BMC Syst Biol., 10: 15.

[18] Denduluria, S., Wang, Z., Liao, Z., Yan, Z., Mohammed, M., Ye, J., 2015. Insulin-like growth factor (IGF) signaling in tumorigenesis and the development of cancer drug resistance. Genes Dis., 2(1):13–25.