The Effect of COL1A and COL3A Gene Polymorphisms on Pelvic Organ Prolapse among the Women of the Belgorod Region

Alexandra S. Ustyuzhina[1,2*], Sergei P. Pakhomov[1], Umeda G. Shokirova[1], Alina V. Matrosova[1], Ibragim M. Soliman[1], Larisa V. Pakhomova[1]

Alexandra S. Ustyuzhina [*1, 2], Sergei P. Pakhomov[1], Umeda G. Shokirova1, Alina V. Matrosova[1], Ibragim M. Soliman[1], Larisa V. Pakhomova[1]

[1]Belgorod State University, Pobeda Street 85, Belgorod, 308015 Russia.
[2]Belgorod Regional Clinical Hospital of St. Joasaph, 8/9 Nekrasov St., Belgorod, 308007, Russia.

Correspondence:
Alexandra S. Ustyuzhina
Belgorod State University, Pobeda Street 85, Belgorod, 308015, Russia
Tell. +79045311115
E-mail: 456647@bsu.edu.ru

ABSTRACT

Relevance: The problem of genital prolapse, despite such a long history of the disease, still does not have a definite solution. Currently, the problem of genital prolapse in women remains relevant due to the high impact on the social part of life. Genital prolapse and impaired function of neighboring organs significantly reduce the quality of life. Every year there are more and more articles linking genital prolapse with connective tissue pathology and with a change in collagen structure. This paper describes the relationship of polymorphisms of the collagen genes COL1A1 and COL3A1 and pelvic organ prolapse in women. This study aimed to analyze the effect of rs1800012 and rs1107946 polymorphisms of the COL1A1 gene, rs1800255 of the COL3A1 gene on the development of pelvic organ prolapse in women of the Belgorod region.

Material and Methods: In 2018 we analyzed 268 women who were residents of the city of Belgorod and the Belgorod region, among which 2 groups were identified. Group 1 (N = 53) included women who had signs of pelvic organ prolapse. Group 2 (N = 215) consisted of women with an objectively proven absence of prolapse. The study was carried out in the gynecological department of Belgorod Regional Clinical Hospital of St. Joasaph.

Results: In our study, it was found that the frequencies of polymorphisms of the COL1A1 and COL3A1 genes in residents of the Belgorod region did not differ from those in representatives of European populations. Thus, in the studied population of Belgorod women, the allele A of the rs1800255 polymorphism of the COL3A1 gene was characterized by a protective effect in relation to the predisposition to pelvic organ prolapse.

Conclusion: In our study, a high association of rs1800255 polymorphism of the COL3A1 gene to pelvic organ prolapse in women of the Belgorod region was confirmed. At the same time, no connection between the rs1800012 and rs1107946 polymorphisms of the COL1A1 gene and genital prolapse was detected.

Keywords: genital prolapse, pelvic organ prolapse, women, collagen, genes, genetic predisposition.

INTRODUCTION

Currently pelvic organ prolapse is considered as a multifactorial disease. Every year, more and more influence is given to the hereditary predisposition of prolapse.

A family history increases the risk of genital prolapse (Chiaffarino et al. 1999; Jack et al. 2006). According to some researchers, there was a five-fold increase of pelvic organ prolapse (POP) risk among the sisters suffering from genital prolapse as compared to the general populationm (Ward et al. 2014).

At the moment, it is increasingly believed that the pathology of connective tissue has a greater impact on vagina walls and ligamentous apparatus of the pelvic organs as compared with trauma during childbirth (Bezmenko & Berlev 2011; Marukhno & Pyatnakovsky 2012). Studies have been described in which dysfunction of the pelvic floor among women is the manifestation of connective tissue dysplasia (Chiaffarino et al. 1999; Akulenko et al. 2017).

According to a large-scale study, a high frequency of genital prolaps was found among nulliparous and parous sisters, which can confirm the hereditary predisposition of this pathology (Buchsbaum et al. 2005).

Every year there are more and more articles linking genital prolapse with connective tissue dysplasia and with collagen structure change. Recent studies have described a high association of pelvic organ prolapse with the COL1A1 and COL3A1 genes in different populations (Chiaffarino et al. 1999; Jack et al. 2006; Akulenko et al. 2017; Kluivers et al. 2009).

Falconer et al. conducted a large immunohistochemical study of ligaments among the women with connective tissue dysplasia and urinary incontinence. According to this study, fibroblast cultures obtained from women suffering from urinary incontinence, contained 30% less collagen than in the groups of healthy women. Collagen of the type I and III was secreted in sufficient quantities and was detected immunohistochemically. Collagen of both types has been modified (Falconer et al. 1994).

According to the data available on NCBI website (The National Center for Biotechnology Information 2020), the greatest influence among type 1 and 3 of collagen genes is noted in the polymorphisms rs1800012 and rs1107946 of

the gene COL1A1, and in the polymorphism rs1800255 of the gene COL3A1.

They noted the association of rs1800012 polymorphism of the COL1A1 gene with genital prolapse and stress urinary incontinence (Cartwright et al. 2015). In the work by Lince S.L. the connection of the COL3A1 gene was not confirmed, only 7% of the main group and 4% of the control group had a homozygous rs1800255 polymorphism of COL3A1 gene (Lince et al. 2014; Akar et al. 2018; Kalenik et al. 2018).

The purpose of this study is to analyze the effect of rs1800012 and rs1107946 polymorphisms of the COL1A1 gene, rs1800255 polymorphism of the COL3A1 gene on the development of pelvic organ prolapse among the women of the Belgorod region.

MATERIALS AND METHODS

In 2018, we analyzed 268 women who were the residents of the city of Belgorod and the Belgorod Region, among which 2 groups were identified. Group 1 (N = 53) included the women who had the signs of pelvic organ prolapse. Group 2 (N = 215) consisted of women with an objectively proven absence of prolapse. The study was conducted in the gynecological department of the Belgorod Regional Hospital.

All participants of the study provided of venous blood into the tubes with 5 ml of anticoagulant (0.5 M EDTA solution), after which they used freezing and stored the samples at the temperature of -20 °C. Blood DNA was isolated using the standard two-stage method of phenol-chloroform extraction and precipitation with ethanol. Genotyping of polymorphic variants rs1800012 (1245G > T) and rs1107946 (C > A) of the COL1A1 gene and SNP rs1800255 of the COL3A1 gene was performed using real-time PCR (PCR Polymerase chain reaction). Molecular genetic studies were carried out at the Department of Biology, Medical Genetics and Ecology of Kursk State Medical University.

In the work they used the methods of multivariate statistics. The database was created and subjected to primary processing in the environment of Excel-2007 (Microsoft). Multivariate statistical analysis was carried out in standard application software packages: Excel-2007 (Microsoft), and Statistika 5.5 (Statsoft).

STUDY RESULTS AND DISCUSSION

We have studied the frequencies of collagen gene polymorphisms among the residents of the Belgorod region and compared them with other European populations (The 1000 Genomes Project Consortium, Nature 2015). The frequencies of minor alleles in the population of the Belgorod region were comparable with those among European populations. For rs1800012 of the COL1A1 gene, the frequency of the minor T allele among the residents of the Belgorod region was 0.170, among European populations it made 0.189, while P (the significance level of differences in allele frequencies between populations) was 0.56. For rs1107946 of the COL1A1 gene, the frequency of the minor allele A among the inhabitants of the Belgorod region was 0.180, among the populations of Europe - 0.138, P was 0.25. For rs1800255 of

the COL3A1 gene, the frequency of the minor allele A among the residents of the Belgorod region was 0.211, among the populations of Europe it was 0.262, P was 0.07. Thus, the frequencies of minor alleles among the residents of the Belgorod region did not differ from those of European population representatives (P > 0.05).

Studying the association of pelvic organ prolapse risk development among the women of the Belgorod region with polymorphic variants of the COL1A1 and COL3A1 genes, four genetic models of SNP relationship with the prolapse phenotype were tested: codominant, dominant, recessive, additive model and overdomination.

The study was made concerning the frequency of allele occurrence of COL1A1 and COL3A1 gene polymorphic variants among the women of the Belgorod region. The results were compared with similar data for European women, according to the project "1000 genomes" (The 1000 Genomes Project Consortium, Nature 2015). The data are presented in table 1.

Table 1: The frequencies of polymorphic variant alleles of the COL1A1 and COL3A1 gene among the women of the Belgorod region (BR) and their comparison with European populations

Gene (SNP ID)	SNP localization in the gene	Minor allele	Minor allele frequencies (MAF) in populations		P3
			BR residents (N)1	Europe populations (N)2	
COL1A1 G>T (rs1800012)	intron	T	0.170 (445)	0.189 (190)	0.56
COL1A1 C>A (rs1107946)	intron	A	0.180 (461)	0.138 (139)	0.25
COL3A1 G>A (rs1800255)	exon	A	0.211 (97)	0.262 (264)	0.07

[1]The number of patient samples successfully progenotyped by SNP;
[2]The data of "1000 Genomes" Project
[3]P- significance level of differences in allele frequencies between populations.

They revealed a statistically significant association of SNP rs1800255 of the COL3A1 gene with a reduced risk of pelvic organ prolapse development (OR = 0.38, 95% CI 0.17-0.84, P = 0.014, log additive genetic model). The minor allele A SNP rs1800255 was more common among healthy women than among the women with pelvic organ prolapse (OR = 0.45, 95% CI 0.22-0.91, P = 0.02) (table 2).

Table 2: Frequencies of polymorphic variant genotypes of the COL1A1 and COL3A1 genes in the studied population

Gene (SNP ID)	Genotypes	Genotype frequencies		Heterozygosity level	
		N	%	H_{obs}	H_{exp}
COL1A1 G>T (rs1800012)	G/G	186	69,4		
	G/T	73	27,2	0.272	0.282
	T/T	9	3,4		
COL1A1 C>A (rs1107946)	C/C	190	67,6		
	C/A	81	28,8	0.288	0.295
	A/A	10	3,6		
COL3A1 G>A (rs1800255)	G/G	58	59,8		
	G/A	37	38,1	0.381	0.333
	A/A	2	2,1		

[1]H_{obs} – actual heterozygosity, H_{exp} – expected heterozygosity

CONCLUSION

Studying the frequency of polymorphic variant alleles of collagen genes among the residents of the Belgorod region, it was found that the frequencies of polymorphisms of the COL1A1 and COL3A1 genes among the residents of the Belgorod region did not differ from those among the representatives of European populations.

Thus, in the studied population of Belgorod women, the allele A of the rs1800255 polymorphism of the COL3A1 gene was characterized by a protective effect in relation to the predisposition to pelvic organ prolapse. The results obtained are consistent with the data of Russian and foreign authors [3,6].

In our study, they confirmed a high association of rs1800255 polymorphism of the COL3A1 gene to pelvic organ prolapse among the women of the Belgorod region. At the same time, no connection between the rs1800012 and rs1107946 polymorphisms of the COL1A1 gene and genital prolapse was detected.

According to the "1000 Genomes" project, the frequencies of polymorphisms of these genes among the women of the Belgorod region and among the representatives of European populations were comparable.

CONFLICT OF INTEREST: None

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