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Review Article

The Role of The Polymorphic Version of C/G Gene Il 17 on The Mechanism of Development of Genital Prolapse after Hysterectomy in Women of The Uzbek Population.

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Summary

The article presents the results of the molecular genetic studies of the IL-17 gene in women with the post hysterectomy prolapse of the genitalia. 121 women aged 26 to 64 years were examined. The results of the study showed that the Getero C/G Homozygote genotypes allele and the IL-17 Polymorphism are significant markers of increased risk of GPAHE development in women of working age in the Uzbek population. (P<0.05). ($\chi 2$ = 110.5; p<0; R = 2086.2; 95% CI 97.3-44734.03) Allele C and functionally favorable C/C genotype are reliable protective markers in relation to the development of pathology ($\chi 2$ = 35, 53; p <0.0009; OR = 0.07; 95%CI 0.02 -0.21; $\chi 2$ = 35.53; p <0.0009; OR = 14.0; 95%Ci 4.8-40.2).

Keywords: Post hysterectomy prolapse genitals, Genetics, IL-17 gene

Review

Recent reports of genital prolapse in nulliparous women, as well as in women after caesarean section, indicate a constitutional factor and a genetic predisposition in the development of this pathology. In this regard, it is important to assess risk factors, as well as preclinical signs of genital prolapse in women of both childbearing and perimenopausal age. For this contingent of women, the choice of optimal treatment strategy is based on determining the pathogenetic factors of the disease. In scientific journals, there are several works on the study of gene expression in the tissues of the pelvic floor in prolapse. There is evidence that the cause of genital prolapse in young women in most cases are hereditary diseases of the connective tissue. The role of the ERα and ERβ genes, as well as their receptors in the development of genital prolapse, has been sufficiently studied [1].

Currently, the IL-17 gene is considered one of the most important regulators of natural and adaptive immunity in the body, especially manifested in various inflammatory diseases and autoimmune nosology's, including diabetes mellitus, as well as oncological diseases [2]. We must admit that molecular genetic studies of the IL17 gene in the pathogenesis of genital prolapse after hysterectomy have not yet been given due attention in the literature. To assess the etiopathogenetic aspects of genital prolapse, the study of genetic aspects will open new aspects of the mechanism of disease development. The aim of our study was to establish the role of the C/G polymorphic variant of the pro-inflammatory cytokine IL17 gene in the pathogenesis of genital prolapse [3]. We examined 121 women aged 26 to 64 years. Among 121 patients, the main group consisted of 91 (75.2%) women with GPGE, and the control group consisted of 30 healthy women without GP (Figure 1).

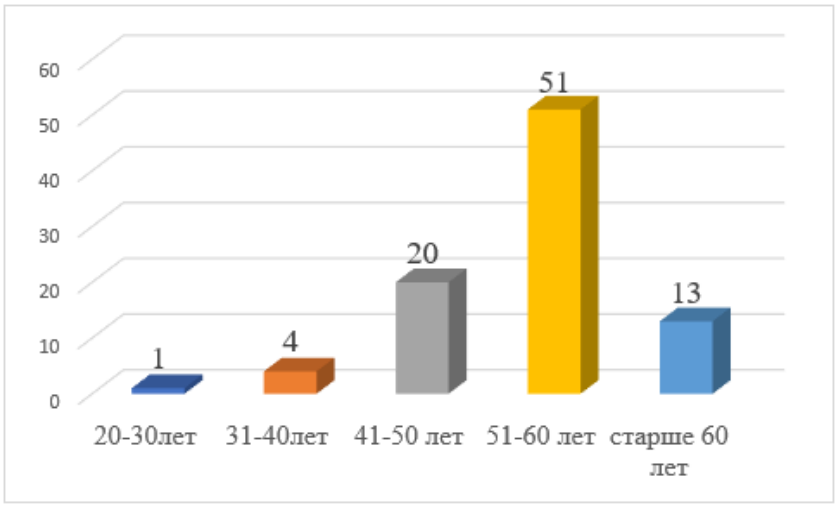

Figure 1: Age aspects of the examined women (abs).

The molecular-genetic examination of biomaterials (DNA) was performed at the premises of the State Institution Republican Specialized Scientific and Practical Medical Centre of Obstetrics and Gynecology. The object and subject of the study were DNA samples of 121 women, the IL23 gene. DNA samples were isolated from peripheral blood lymphocytes according to a modified method. The concentration and purity of the isolated DNA were evaluated by measuring the optical density of DNA-containing solutions at a wavelength of 260 and 280nm against HU on a Nano Drop 2000 spectrophotometer (USA) [4].

The genotyping of the IL17 gene polymorphism was carried out on a real-time PCR amplifier Rotor Gene 6000 Model 65H0-100 (Australia), using the test system of the company "Synthol", Cat. No.-NP_555_100_RG (Russia), according to the manufacturer's instructions. Statistical analysis of the results was conducted using a package of "OpenEI 2009, Version 2.3" statistical software [5]. The frequency of variants of alleles and genotypes (f) was calculated by the formula: f=n/2N and f=n/N. The results of molecular genetic studies of the C/G of the pro-inflammatory cytokine IL17 gene in the examined patients are presented in (Table 1) [6].

Table 1: The frequency of distribution of allelic variants and polymorphism (rs 612242) of the IL-17 gene in women with GPAHE and in the control group of healthy women.

No.	Group	Allele Frequency				Frequency Distribution of Genotypes					
		C		G		C/C		C/G		G/G	
		*n	%	*n	%	n	%	n	%	n	%
1	Main group n=91 (182)	91	50*	91	50*	0		91	100*	0	0
2	Control group n=30 (60)	56	93,3	4	6,6	27	90	2	6,6	1	3.3

Note*: N is the number of examined patients; *n is the number of studied alleles; *is the indicator of reliability in relation to the control group (P<0.05).

The results of molecular genetic studies of the gene (rs 612242) C/G of the IL-17 gene showed that the C functional allele in the main group of women with GPAHE was detected in 50% of cases (91/182), and in the control group of women without GPAHE was found in 93.3% of cases (56/60), which is 1.8 times higher than in the main group ($\chi 2$=35.5; p<0.0009; OR=0.07; 95%CI 0.02-0.21). The "G" mutant allele was also detected in 50% of cases in the main group of women with GP (91/182), while in the control group it was detected in 6.6% of cases (4/60), which was 11.4 times lower compared to with the main group. ($\chi 2$=35.53; p<0.0009; OR=14.0; 95%CI4.8-40.2); (Table 2) [7].

Table 2: The results of molecular-genetic analyzes were analyzed depending on the co-morbidity of women with GPAHE.

Alleles and Genotypes	Number of Examined Alleles and Genotypes		Statistical Difference
	Main group	Control	
Allele C	91	56	χ2=35.53; p<0.0009; OR=14.0; 95%CI 4.8 -40.2
Allele G	91	4	
Genotype C/C	0	27	χ2=110.5; p<0; OR=0; 95%CI 0.0-0.01
Genotype C/G	91	2	χ2=110.5; p<0; OR=2086.2; 95%CI 97.3 -44734.03
Genotype G/G	0	1	χ2=110.5; p<0; OR=0.11 95%CI 0.00-2.71

We also analyzed associations of the IL17 gene polymorphisms. Thus, the analysis of the polymorphism of the genotypes (rs612242) C/G of the IL-17 gene showed that the functional C/C genotype of the IL-17 gene in the control group of healthy women was detected in 90% of cases (27/30), while in the main group of women with GPGE in our cases was not determined (χ2=110.5; p<0; OR=0; 95%CI 0.0-0.01). It was interesting that the heterozygous variant C/G of the IL-17 gene in the main group was determined in all women with GPAHE, which accounted for 100% (91/182) of cases, while in the control group, it was determined in 2 out of 30, which amounted to 6 .6% of cases, which was 15.2 times lower compared to the main group. (χ2=110.5; p<0; OR=2086.2; 95%CI97.3 -44734.03); The data obtained were statistically significant (P<0.05) [8].

Statistical analysis showed the significance of this difference in the frequency of detection of the heterozygous genotype. Whereas the homozygous variant of the G/G genotype of the association of polymorphism (rs 612242) C/G of the IL-17 gene was found in 1 woman of the control group, which was 3.3% (1/30), this genotype was not determined in women of the main group. (χ2=110.5; p<0; OR=0.11 95%CI 0.00-2.71). The data obtained indicates that the carriage of the unfavorable allele G(rs612242) of the IL-17 gene can be a diagnostic marker of the risk of developing genital prolapse after hysterectomy, which increases its risk by 14 times (OR=14.0) [9].

Indicators of the Difference in the Frequency of Occurrence of Alleles and Genotypes of the rs612242 C/G Polymorphism of the IL-17 Gene in the Main and Control Groups

The results of molecular-genetic analyzes were analyzed depending on the co-morbidity of women with GPAHE (Figure 2). The comparison of the obtained results with co-morbidity in women with GP showed that they were most often diagnosed with urinary tract infections (chronic pyelonephritis, cystitis)-39.5%, metabolic syndrome (obesity)-33.3%, anemia-29.6%, and lower extremity varicose vein disease-in 22.2%, respectively [10]. In our opinion, co-morbidity in women with GPAHE plays an important role in the clinical course of the disease. An imbalance in the immune system in the production of pro-inflammatory cytokine is caused by chronic inflammatory diseases caused by opportunistic microorganisms against the background of the metabolic syndrome, with obesity [11].

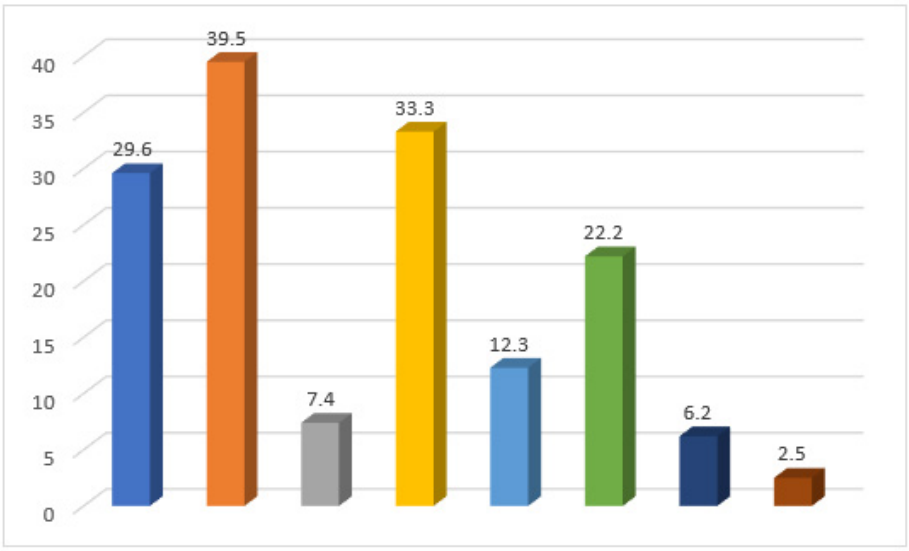

Figure 2: The co-morbidity rate in women with GPAHE (%).

Analysis of the obtained results indicates a significant association of the unfavorable variant allele of "G" polymorphism (rs612242) of the IL-17 gene, which contributes to the replacement of C with G in the amino acid sequence, with the development of genital prolapse against the background of an infectious-inflammatory process of the urogenital system and metabolic syndrome. It was found that the high risk of developing genital prolapses after hysterectomy in women, and in the case of the presence of a variant allele of the G polymorphism in the genome, is increased by 14 times (OR = 14). It should be noted that the heterozygous C/G genotype of the rs612242 polymorphism of the IL-17 gene is a genetic determinant that is an increased risk factor for predisposition to the development of GPGE, which increases its risk by 2086.2 times (OR = 2086.2) (P<0.05) [12].

The analysis of the data obtained indicates that with the carriage of the unfavorable allele G of the IL-17 gene, the risk of developing GPAHE can be observed in women with metabolic syndrome (obesity) and a disease of the genitourinary system, which requires close attention of dispensary registration in women's offices in primary health care. Also, the disease of the vascular system, endocrinopathy, blood diseases, which are provoking factors that contribute to the development of GPAHE, are of high importance [13].

Thus, the G allele and hetero/homozygous genotypes of the C/G polymorphism of the IL-17 gene are significant markers of an increased risk of developing GPAHE in women of working age in the Uzbek population. (P<0.05). (χ2=110.5; p<0; OR=2086.2; 95%CI 97.3-44734.03) The C allele and the functionally favorable C/C genotype are significant protective markers for the development of pathology (χ2=35, 53; p<0.0009; OR=0.07; 95%CI 0.02 -0.21; χ2=35.53; p<0.0009; OR=14.0; 95%CI 4.8-40.2). An analysis of the results obtained indicates that women with the allelic variant G and heterozygous C/G of the IL-17 gene have a risk of developing genital prolapse after hysterectomy against the background of urinary tract infection and metabolic syndrome [14].

Thus, the results of published in the literature and our own studies indicate that the IL-17 pro-inflammatory cytokine plays an important role in the development of GPAHE in Uzbek women. IL-17 is a membrane glycoprotein, which is the main agent that induces the maturation of hematopoietic precursors. Its receptor and interleukin play an important role in many inflammatory and autoimmune diseases, which we have identified in somatic pathologies preceding genital prolapse after hysterectomy [15].

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