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Research Aticle

Influence of the Rs2236479 Polymorphism Gene COL18A1 on the Development of Pelvic Floor Dysfunction in Women

Vishnevskii DA[1]*, Kasyan GR[1], Akulenko LV[2], Pushkar D Yu[1]

[1]*Department of Urology of Moscow State Medical and Stomatology University, AI Evdokimov Ministry of Health of the Russian Federation, Moscow, Russia*

[2]*Department of Medical Genetics of Moscow State Medical and Stomatology University AI Evdokimov Ministry of Health of the Russian Federation, Moscow, Russia*

***Corresponding author:** Vishnevskii DA, Department of Urology of Moscow State Medical and Stomatology University, AI Evdokimov Ministry of Health of the Russian Federation, Moscow, Russia

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Introduction

Under the pelvic dysfunction understand the state in which disrupted the normal position of the pelvic organs, as well as dysfunction of urine and calla. Under the pelvic prolapse or prolapse of the pelvic organs (POP) understand the hernial protrusion of the pelvic organs in the vaginal region [1]. Similar indicators are found in Europe [2], the states of the Middle East [3] and North Africa [4]. Under the stress form of urinary incontinence understand the involuntary loss of urine during exercise (coughing, laughing, performing physical exercises). In turn, the stress form of urinary incontinence is also very common. The high prevalence of these diseases makes pelvic prolapse and stress urinary incontinence (SUI) a serious medical, social and economic problem, requiring a deep study of the ethological aspects of the problem and the development of new and most optimal treatment methods. POP and SUI are a consequence of violations of the supporting apparatus of the pelvic floor. These diseases are multifactorial pathology. The etiology of POP and SUI consists of environmental factors (multiple births, traumatic labor, large fetus, etc.) [5], concomitant multifactorial pathologies (bronchial asthma, chronic bronchitis, obesity, etc.) [6]. A large number of described family cases of POP and SUI prompted some researchers to put forward a hypothesis about the existence of a hereditary predisposition to these diseases. In order to confirm / refute this hypothesis, a number of studies were undertaken using clinical, genealogical, population-statistical and twin methods of genetic research, which resulted in the fact that POP and SUI are pathologies of a multifactorial nature with a very significant contribution of genetic and environmental factors to their etiology (43% and 57% respectively) [7]. Thus, a framework was created to search for specific molecular genetic markers that determine a predisposition for the development of pelvic dysfunction in women. Currently, searches for genetic markers are being conducted among the genes responsible for the synthesis and assembly of connective tissue elements (collagen fibers, elastic fibers, and the endocervical matrix). An important component of the connective tissue matrix is collagen fiber. The most important for supporting the structures of the small pelvis are collagen proteins of I and III types. Studies conducted to verify the association of collagens type I and III have given very contradictory results. A large meta-analysis devoted to the study of collagen protein genes was performed in 2014. R.M. Ward et al. Presented very interesting results [8]. As a result of this meta-analysis, the association of the rs1800255-A / A polymorphism of the COL3A1 gene with the development of POP was identified. This meta-analysis did not confirm the association of the polymorphic variant rs1800012 of the COL1A1 gene with the development of POP. However, already in 2015, Cartwright and co-authors conducted their meta-analysis on the association of collagen proteins with PTO [9]. This study did not confirm the association of the rs1800255-A / A polymorphism of the COL3A1 gene with the POP but revealed an association of pelvic prolapse with the polymorphic rs1800012 variant of the COL1A1 gene. Such a discrepancy is most likely due to the fact that pelvic dysfunction is a multifactorial disease, and when searching for the association of polymorphisms with POP and SUI, it is necessary to take into account all external factors and associated diseases. Collagen of the eighteenth type is represented to a lesser extent than collagen proteins of the first and third types. Nevertheless, the epidemiological study conducted by Allen-Brady identified rs2236479 polymorphism in the COL18A1 gene as a potential marker of pelvic floor dysfunction [10]. These data were the reason for conducting this study.

Materials and Methods

For the study were recruited two groups of patients. The first group is a study group that included patients with pelvic prolapse or \ and a stressful form of urinary incontinence. This group consisted of 150 patients. Of these, 36 patients suffered POP, 57 patients - SUI and 57 patients - POP and SUI. All patients were aged from 40 to 70 years (mean age 65 ± 2 years). The second group is the control group that included patients without pelvic dysfunction. This group recruited 100 patients with pyelonephritis, cystitis, urolithiasis, etc. The average age of patients in the control group averaged 64.9 ± 2 years. Patients in both groups had one or several external environmental risk factors, for example, two or more births through the birth canal, traumatic labor, childbirth over 4000 years, excessive physical activity, diseases accompanied by an increase in abdominal pressure (bronchial asthma, chronic bronchitis, chronic constipation), the presence of operations on the pelvic organs.

The exclusion criteria for patients from both groups were the hereditary Marfan and Ehlers – Danlos syndromes, as well as patients with mental illness. All 250 patients gave written consent to participate in the study. As a biological material for genotyping, the buccal epithelium was collected from all study participants. The epithelium was collected in a special plastic tube. Before the delivery of biological samples of saliva, all patients refrained from eating food, fluids, and smoking for at least 1 hour. Immediately before donating the patient's saliva, the cheek mucosa was chewed for 5–10 seconds, then 3-4 ml of the saliva was collected into a sterile tube. The tubes were numbered and frozen until further transport to the laboratory.

Laboratory Research

The implementation of the design of the primers and the genotyping of the patients of the studied and control groups was carried out in the molecular genetic laboratory of the FSBI FNCC PCM FMBA Russia using the online system Primer-BLAST and the Sanger sequencing method, respectively. SNIP rs2236479 has 2 allelic states, the major allele G, the minor allele A. According to studies with more than 200 people, the frequency of the allele G varies from 0.47 to 0.68. For Sanger genotyping, the following primer pair was selected for the COL18A1 (rs2236479) marker: forward primer Cl18Af2 ACAGTGTTTTAGAGGCGGAAT and reverse primer Cl18Ar2 AGCCTGTGCCGGTTCCTG.

Statistical Analysis

To compare the quantitative data in two unrelated samples, the Mann-Whitney U-test was used. For comparison of nominal variables in two unrelated sets, Fisher's exact test was used. The level of significance (p) was assumed to be 0.05 in all comparisons.

Results

The results of the polymorphism genotyping for the study group and the rs2236479 control group are presented in Table 1. The distribution of genotypes and alleles of the study and the control group are presented in the diagrams in Figures 1& 2. Statistical analysis comparing the two groups did not reveal significant differences between the study group and the control group. Thus, the association between the rs2236479 polymorphism of the COL18A1 gene and pelvic dysfunction has not been established.

Table 1: Results of polymorphism genotyping for the study group and the control group rs2236479.

Alleles and genotypes	The frequency of alleles and genotypes of the rs2236479 polymorphism of the COL18A1 gene in the bis-studied and control groups				p
	study group (n=150)		Control group (n=100)		
	N	%	N	%	
G	140	93,3	95	95	p<0,05
A	33	22	29	29	p<0,05
GG	117	78	71	71	p<0,05
GA	23	15,3	24	24	p<0,05
AA	10	6,7	5	5	p<0,05

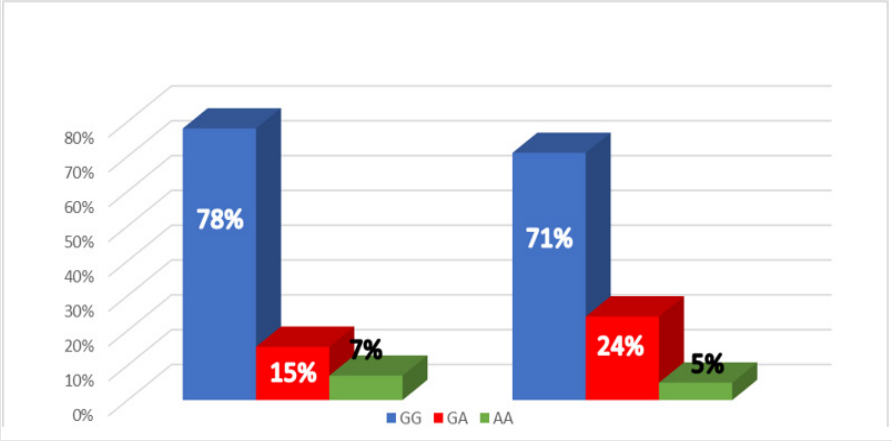

Figure 1: Genotype distribution of the rs2236479 polymorphism of the COL18A1 gene in control study groups.

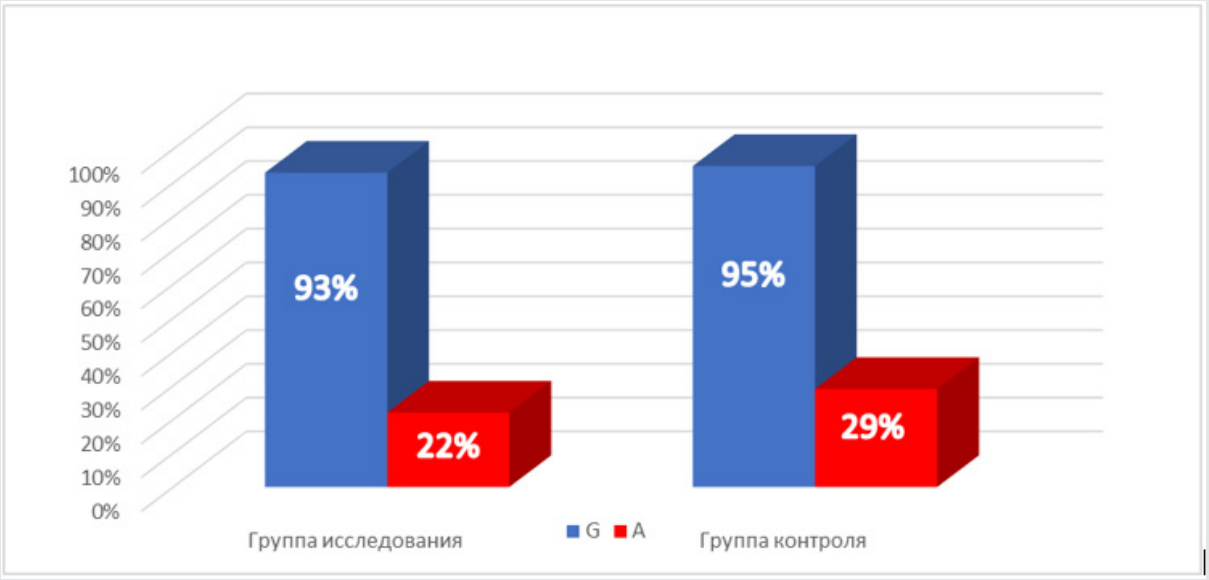

Figure 2: Distribution of alleles of the rs2236479 polymorphism of the COL18A1 gene in control study groups.

Discussion

In 2011, an epidemiological study by Allen-Brady identified rs2236479 polymorphism in the COL18A1 gene as a potential marker of pelvic floor dysfunction [10]. To test the association of the above polymorphism with pelvic dysfunction, a study was conducted in which 250 patients were included (150 study groups and 100 control group patients). Both groups were similar in external risk factors associated with multifactorial pathology and by age. For genotyping, the Sanger method was used, which is the gold standard for the study of single polymorphisms. As a result of the study, the association of the studied polymorphism with pelvic dysfunction was not confirmed. Also, no association of this polymorphism with isolated prolapse was revealed, only with incontinence and a combination of POP and SUI.

Conclusion

There is no association of the polymorphic rs2236479 variant of the COL18A1 gene with pelvic dysfunction. Further development of this polymorphism as a marker of pelvic dysfunction is not advisable.

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