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TUXUMODONLAR POLIKISTOZ SINDROMIDA YORDAMCHI REPRODUKTIV TEXNOLOGIYALARNING SAMARADORLIGNI BAHOLASH

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✓ ***Rezyume***

Mualliflar TPS bilan kasallangan 106 bemorda CYP19A1 genini (rs 2470152) o‘rganishdi. Olingan natijalan shuni ko‘rsatdiki TPS bor bemorlarning 17 foizida gomozigotli yovvoyi tip genotip, 48,1 foizida geterozigot GA genotipi bo‘lgan, AA mutant genotipli gomozigotli bemorlarning 35,9 foizi borligi aniqlangan.

Kalit so‘zlar: tuxumdonlar polikistoz sindromi, reproduktiv yosh, metabolik sindrom, yordamchi reproduktiv texnologiyalar.

ОЦЕНКА ЭФФЕКТИВНОСТИ ВСПОМОГАТЕЛЬНЫХ РЕПРОДУКТИВНЫХ ТЕХНОЛОГИЙ ПРИ СИНДРОМЕ ПОЛИКИСТОЗА ЯИЧНИКОВ

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✓ ***Резюме***

Авторами было проведено исследование гена CYP19A1 (rs2470152) у 106 больных СПКЯ. Установлено, что 17% больных имеют гомозиготный генотип дикого типа, 48,1% больных имеют гетерозиготный генотип GA, 35,9% больных имеют гомозиготный мутантный генотип AA у больных СПКЯ.

Ключевые слова: синдром поликистозных яичников, репродуктивный возраст, метаболические нарушения, вспомогательные репродуктивные технологии.

EVALUATION OF THE EFFICACY OF ASSISTED REPRODUCTIVE TECHNOLOGIES IN POLYCYSTIC OVARIAN SYNDROME

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✓ ***Resume***

Authors was held study of the CYP19A1 gene (rs2470152) in 106 patients with PCOS. It was found that 17% of patients have a homozygous wild-type genotype, 48.1% of patients with a heterozygous GA genotype, 35.9% of patients with a homozygous AA mutant genotype in patients suffering from PCOS.

Keywords: polycystic ovary syndrome, reproductive age, metabolic disorders, assisted reproductive technologies.

Relevance

PCOS is an extremely heterogeneous and complex disease [1]. The genetic basis of PCOS varies between families and within families, but is associated with a common pathway [2]. Due to complexity and heterogeneity, a single gene or related genes in the same family have not been described [2,3]. The genetic predisposition to different genes differs in patients from the same family [3]. Recently, intrauterine programming has been suggested as a predisposition factor for PCOS [3,4]. Genome screening to find a candidate gene in a disease as complex as PCOS is unrealistic. Linkage analysis in

such families always gives a negative result [4]. In this disease, case-control studies with large population sizes and genome-wide association studies (GWAS) are useful to look for possible associations. Parental analysis in such diseases is often impractical; however, the known risk of disease can be estimated [5].

The CYP19 gene responsible for the p450 aromatase required for estrogen production is located on chromosome number 15q21.2.73 Lower aromatase activity has been reported in both obese and lean women with PCOS [6,7].

The “q” arm of the X chromosome contains the AR gene, which consists of 11 exons and encodes a 90 kb three-domain protein. 74 Mutations and structural abnormalities of the gene have been reported to cause PCOS [7]. Inactivation of the "X" chromosome leads to disruption of the cellular pathway, causing an increase in the level of the hormone androgen, which leads to PCOS [8]. Since the AR gene is located on the X chromosome, a change in one copy of the gene is enough to cause pathology [9]. GWAS also reported a new gene variation that is the cause of PCOS.

The SHBG gene is located on chromosome 17p13-p12. SHBG synthesizes a protein of 373 amino acids [10]. The protein product SHBG controls the level of sex hormones in the body by binding to androgens, predominantly estrogens and testosterone. Most of SHBG is synthesized by hepatocytes in the liver. SHBG synthesis by hepatocytes is controlled by several metabolic factors, such as androgens and insulin [11]. SHBG concentration is lower in women with PCOS, which is mainly due to the inhibitory effect of hyperinsulinemia on SHBG synthesis. Single nucleotide polymorphism in many studies has been described that the gene SHBG is strongly associated with PCOS [12].

Purpose of the study: Study of the features of allelic variants of CYP19A1 gene polymorphism in women with PCOS.

Material and methods

All 106 observed patients underwent a genetic study of gene polymorphism CYP19A1. All 106 patients were divided into 2 groups: the first group - patients with metabolic syndrome (n=60) (MS+), the second group - patients with PCOS without metabolic syndrome (n=46) (MS-). The control group consisted of 52 healthy volunteers with no history of predisposition to PCOS.

Results and discussions

In the process of studying the distributionallelic variants of CYP19A1 gene polymorphismin patients with PCOS, it was found that the homozygous GG genotype was registered in MC+ patients with PCOS in 25% of cases, while only in MC-patients with PCOS in 4.3% and 40.4% in the control group. The heterozygous genotype (GA) was 42.3% in the control group, 38.3% in the first group, and the highest rate was in the second group 61% (MS (-). And it was also found that the AA genotype with a homozygous mutant variant was significantly low in the control group - 17.3%, in the other two groups (MC+ and MC-) the result was significantly different from the control group (36.7% and 34.7%) (Figure 1).

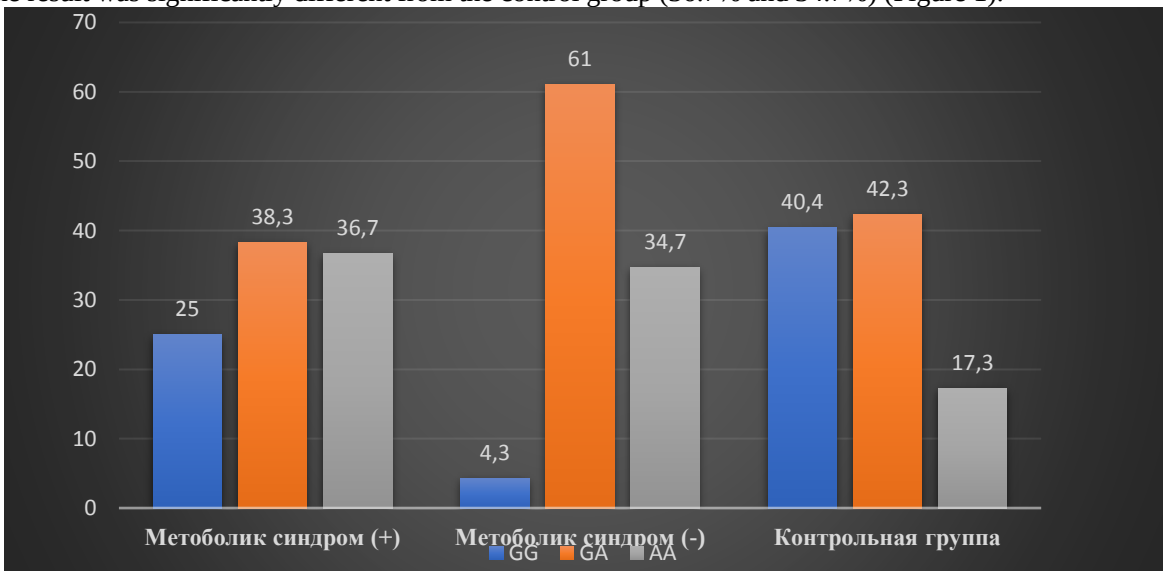

Fig.1 The result of the study of the distribution of the CYP19A1 gene with different polymorphic variants in different groups

According to the percentage of the CYP19A1 gene, depending on the degree of occurrence, the normal G-allele was observed in 44.2% of MS+ PCOS patients. On the other hand, this figure was 34.8% in PCOS MS patients and 61.1% in the control group. The mutant allele was found in 38.9% of patients in the control group, while in the first and second groups it was 55.8% and 65.2%, respectively.

As for the distribution of wild variant genotypes for the CYP19A1 gene as a percentage for all patients with PCOS and the control group, it was found that the second group prevailed over the first (16% and 40.4%, respectively). The heterozygous genotype showed almost the same result in the two groups of subjects (48.1% and 42.3%, respectively). Although the heterozygous genotype was an inducing factor in terms of influencing the development of PCOS, this variant was not significant. (chi2=0.47; OR=1.2; 95%CI:0.71 - 2.09 $p < 0.5$). However, when studying the mutant form of AA, it was found that it is detected in most cases in patients, in contrast to the control group, and is confirmed as a significant risk factor in the development of PCOS. (respectively 35.8% and 17.3%, chi2=5.74; OR=2.7; 95%CI: 1.17–6.06, $p<0.02$). (tab. 1).

Table 1

Results of genotyping of CYP19A1 gene polymorphism in patients with PCOS and healthy controls.

Alleles and genotypes	Number of examined alleles and genotypes				Chi2	P	RR	95%CI	OR	95%CI
	Main group		Control group							
	N	%	N	%						
G	85	40.1	64	61.1	12.8	p<0.001	0.75	0.63 - .88	0.4	0.26 - 0.67
A	127	59.9	40	38.9	12.8	p<0.001	1.33	1.13 - .57	2.4	1.48 - 3.86
G/G	17	16.0	21	40.4	11.3	p<0.001	0.6	0.41 -0.87	0.3	0.13 - 0.60
G/A	51	48.1	22	42.3	0.47	p<0.5	1.1	0.88 - 1.36	1.2	0.65 - 2.5
A/A	38	35.8	9	17.3	5.74	p<0.02	1.3	1.1 - 1.62	2.7	1.17 - 6.06

During the study, when divided into groups in patients with PCOS, it was found that the mutant form (AA) in patients with metabolic syndrome is an important and reliable factor in the development of PCOS. (Chi2=5.2; OR=2.76; 95% CI:1.1 - 6.7; $p = 0.02$). In particular, the homozygous form of the genotype - the "wild" variant (GG) with a significant difference prevailed in the control group (40.4%), this variant was 25% in PCOS patients with MS (+). The mutant form of the homozygous genotype was found in PCOS patients with metabolic syndrome in 36.7%, and the heterozygous genotype in 38.3%. In healthy individuals, this figure was 17.3 and 42.3%, respectively (Table 2).

Similarly, a mutant homozygous form of the CYP19A1 gene plays a significant role in the development of PCOS in patients without metabolic syndrome (chi2 = 3.9; OR = 2.5; 95% CI1 - 6.53; $p < 0.05$). In addition, a mutant variant of the CYP19A1 gene (AA genotype) was registered in patients with MS (+) almost twice as often as in healthy patients (34.8% and 17.3%). Similarly, the heterozygous variant of the genotype was more common in the first group than in the second (60.9% and 42.3%, respectively). As expected, the normal homozygous CYP19A1 gene had a significant advantage in terms of occurrence in healthy people (4.3% of metabolic syndrome patients with PCOS and 40.4% in healthy people) (Table 3).

Table 2

Results of genotyping of CYP19A1 gene polymorphism in PCOS patients with metabolic syndrome and healthy individuals.

Alleles and genotypes	Number of examined alleles and genotypes				Chi2	P	RR	95%CI	OR	95%CI
	PCOS with metabolic syndrome		Control group							
	N	%	N	%						
G	53	44.2	64	61.1	6.7	p=0.01	0.7	0.56 - 0.92	0.5	0.29 - 0.84
A	67	55.8	40	38.9	6.7	p=0.01	1.38	1.08 - 1.77	2.0	1.18 - 3.45
G/G	fiftee n	25.0	21	40.4	3.5	p<0.1	0.6	0.24 - 1.65	0.5	0.25 - 1.03
G/A	23	38.3	22	42.3	0.18	p<0.7	0.9	0.64 - 1.32	0.85	0.39 - 1.80
A/A	22	36.7	9	17.3	5.2	p=0.02	1.5	1.1 - 2.1	2.76	1.1 - 6.7

Table 3 Results of CYP19A1_2 gene polymorphism genotyping in patients with PCOS and healthy individuals without metabolic syndrome

Alleles and genotypes	Number of examined alleles and genotypes				Chi2	P	RR	95%CI	OR	95%CI
	PCOS without metabolic syndrome		Control group							
	n	%	N	%						
G	32	34.8	64	61.1	13.9	p<0.001	0.5	0.40 - 0.76	0.33	0.18 - 0.59
A	60	65.2	40	38.9	13.9	p<0.001	1.8	1.3 - 2.49	3.0	1.67 - 5.37
G/G	2	4.3	21	40.4	17.6	p<0.001	0.1	0.04 - 0.56	0.67	0.01 - 0.30
G/A	28	60.9	22	42.3	3.4	p=0.06	1.5	0.96 - 2.32	2.1	0.94 - 4.76
A/A	16	34.8	9	17.3	3.9	p<0.05	1.6	1.04 - 2.33	2.5	1 - 6.53

The distribution of genotypes in the studied polymorphic loci was examined for compliance with the Hardy-Weinberg equilibrium. In the main group of CYP19A1 gene genotypes, no deviations from the level of the expected result were observed (Table 4).

Table 4 Correspondence of the genotype of the CYP19A1_2 gene polymorphism to the Hardy-Weinberg equation in the main group of patients.

Main group					
alleles	Allele frequency				
G	0.4				
A	0.6				
Genotypes	Genotype frequency		Xi2	p	df
	observable	expected			
G/G	0.16	0.16	0		
G/A	0.48	0.48	0		
A/A	0.36	0.36	0		
Total	one	one	0	0.208	one

Conclusion

In this way, the study showedthat the mutant alleles were found to be significantly higher in the observed patients compared to the control group. When distributing in terms of CYP19A1 to the main group into MC (+) and MC (-) and compared with the control group, it was found that the homozygous mutant genotype was detected more in the MC (+) and MC (-) group compared to the control group. With this, we can conclude that the homozygous mutational form of the CYP19A1 gene plays a convincing inducible role in PCOS and the result was significant (chi2 - 5.74; $p<0.02$ in the main group; chi2=5.2; $p=0.02$ in patients with metabolic syndrome and chi2=3.9; $p<0.05$ in patients without metabolic syndrome).

However, the study did not reveal an induced effect on the heterozygous genotype in the development of PCOS (chi2<3.85; $p>0.05$). At the same time, the homozygous wild-type variant played a protective role in terms of the appearance of PCOS in the main group, as well as in the MC (+) and MC (-) groups ($OR\geq0.5$). When it comes to the Hardy Weinberg equation, we found no significant difference between the expected and observed results in the main group. Estimates of polymorphism prediction efficiency, as already mentioned, showed only 0.6, which means that the prediction efficiency was not reliable in terms of mutant allele and genotype.

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