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The Role of Interleukin-4 Gene rs 1800629 (C-589T) Polymorphism in Pregnant Women's Prevention of COVID-19

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Abstract Since the beginning of the pandemic, COVID-19 has caused serious concern among all people, especially pregnant women. Due to the physiological conditions of the cardiovascular, respiratory, and immune systems during pregnancy, it is known that women suffer from any infectious and non-infectious diseases more severely than women of other contingents. During the development of COVID-19, it causes acute respiratory syndromes, which in turn causes the development of pathological conditions in the function of other organs. The immune response of the body plays an important role in the development of all serious complications. The main reason for the weakening of immunity is the genetic factor. **The purpose of the work:** to study the role of the IL 4 gene rs 1800629 polymorphism in the pathogenesis of pneumonia with the etiology of COVID-19. **Materials and methods.** The materials of our research work conducted in the departments of pregnancy diseases of maternity hospitals of Andijan region are based on the clinical analysis and diagnostic results of women infected with COVID-19 at different stages of pregnancy. Molecular genetic studies It was conducted in the Department of Molecular Medicine and Cell Technologies of the Republican Specialized Hematology Scientific and Applied Medical Center. Analysis of IL4 gene rs 1800629 and polymorphism was performed using a case-control model. **Conclusion:** our results allow us to conclude that the homozygous C/C genotype of the IL4 gene plays an important role in the pathogenesis of the exacerbation of Covid-19, the origin of pneumonia and the development of dangerous complications. This genotypic variant of the IL 4 gene can cause a significant increase of more than 3 times the risk of relapse and more severe forms of COVID-19. The homozygous G/G genotype has been shown to have a protective effect against this viral disease.

Keywords Immune reactivity, ARDS, Gen, Polymorphism, Cytokine storm syndrome, Interleukin-4 (IL-4), Pneumonia, SARS-CoV-2, Relapse

1. Enter

The coronavirus disease (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a global public health emergency. According to the World Health Organization, as of February 8, 2022, 394,381,395 people have been diagnosed with COVID-19, and 5,735,179 people have died [5]. Although the current epidemic situation has eased somewhat, new mutant strains continue to emerge, posing a major public health challenge worldwide [4].

Women who are pregnant or have recently become pregnant are more likely to contract COVID-19 than non-pregnant people. [6,7] Among women Although the absolute risk of serious complications from COVID-19 is low, pregnant women have a significantly higher risk of severe complications than non-pregnant women. [1,2,3] This is mainly due to the physiological changes in pregnancy conditions: changes in the immune system, cardiovascular system, respiratory system are shown [2,3]. Also, in recent literature, it has been emphasized that coronavirus infection is associated with gene modification, especially with polymorphism of genes responsible for immunity. Immune-pathogenic mechanisms are also actively involved in the development of ARDS in coronavirus infection, which

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is associated with the immunological response, which is also called "cytokine storm syndrome" [9]. Among them, Interleukin (IL)-4 is the main component of the immune system. It is necessary to regulate the response to allergen by controlling isotype switching of antibodies in B lymphocytes to IgG and IgE classes [8].

Although the secretion of the cytokine storm in the disease of COVID-19 is generally similar to that of SARS-CoV and MERS-CoV infections, there are some important differences, for example: in the concentration of T-helper-2 (Th2) cytokines [10]. SARS-CoV-2 infection differs from other coronaviruses by different concentrations of Th2 cytokines. IL-4 and IL-10 are the main cytokines of Th-2 lymphocytes and have immune regulatory functions by inhibiting Th-1 cytokine secretion [10,11]. Interleukin-4 (IL-4), an anti-inflammatory cytokine that activates its receptor and induces cell-cell interactions, plays an important role in regulating various signaling pathways, including cell proliferation. It is activated by IL-4 [12,13]. Activation of IL-4 secretion and stimulation of IL-4 receptors reduce the secretion of other inflammatory cytokines, including TNF-α, IL-1, and PGE, as well as increase low-density lipoprotein (LDL) oxidation, resulting in reduced inflammation [14,13]. In addition, IL-4 activated by Th2 cells has been shown to induce apoptosis by stimulating the signal transducer and activator of transcription (STAT) signaling pathway [15]. From the research and evidence on SARS-CoV-2, it is known that the production of Th2, Th1/Th17 cells and antibodies is significantly increased in the body of patients infected with COVID-19, but the high level of Th2 indicates that patients need intensive treatment. shows [16]. Hence, one of the inflammatory pathways in the body during the COVID-19 disease: the virus increases apoptotic activity by increasing Th2 and IL-4 cells and inducing the activity of the JAK-STAT6 signaling pathway [15].

2. Purpose of the Study

To study the role of IL-4 gene rs 1800629 polymorphism in the pathogenesis of pneumonia with the etiology of COVID-19 in pregnant women.

3. Material and Methods

Venous blood and DNA samples were extracted from 110 women with various severity of COVID-19. Of these, 70 are pregnant women with a more severe (pneumonia-complicated) form of COVID-19, and 40 are pregnant women who have passed the disease without complications. The control sample consisted of 105 conditionally healthy donors. A comparative analysis of the IL-10 gene rs1800896 polymorphism was performed using a case-control model (comparison of two comparative samples). Biomaterial sampling was performed using standard vacuum tubes containing EDTA-K3 anticoagulant (Vacutainer Becton Dickinson International, USA). For PCR studies, genomic DNA was isolated using the AmpliPrime RIBO-prep reagent kit (NextBio, Russia). Genotyping was performed using LITEX (Russia) reagent kits according to the manufacturer's instructions. Amplification was performed using a Rotor-Gene 6000 thermal cycler (Corbett Research, Australia).

Statistical processing of the obtained results was carried out using statistical package of "STATISTICA 10.0" applications.

4. Results and Discussion

Tables 1 and 2 analyze the distribution frequencies of alleles and genotypes of the rs 1800629 polymorphism of the IL 4 gene. It shows results from the total group, subgroups and a control group.

Table 1 shows that the prevalence of G and C alleles in patients was 72.3% and 27.7%, and the control group was 83.3% and 16.7%, respectively. Among patients, the chance of detecting a weak C allele was significantly increased by 3 times compared to the control group (χ^2 =7.6; r =0.01; OR=1.9; 95% CI:1.21-3.05).

The study of the distribution of genotypes showed that the dominant genotype in the studied patient groups and the control group was the G/G homozygous genotype, the frequency of which was 55.5% and 70.5%, respectively. With test statistics χ^2 =5.2; P=0.03; OR=0.5; 95% CI: 0.3-0.1, suggesting a possible protective effect of this genotype in women with COVID-19.

Table 1. Distribution frequency of alleles and genotypes of rs 1800629 polymorphism of the IL4 gene in groups of pregnant women with COVID-19 and controls

Num	groups	Allele frequency				Frequency distribution of genotypes					
		G		C		G / G		G / C		C/C	
		n	%	n	%	n	%	n	%	n	%
1	Main group n=110 (220)	159	72.3	61	27.7	61	55.4	37	33.6	12	11.0
A	pregnant women with severe (pneumonia-complicated) COVID-19 (n=140)	101	72.1	39	27.9	37	52.8	27	38.6	6	8.6
B	Pregnant women with mild COVID-19 n = 40 (80)	58	72.5	22	27.5	24	60.0	10	25.0	6	15.0
2	Control group n= 105 (210)	175	83.3	35	16.7	74	70.5	27	25.7	4	3.8

Table 2. Differences in the frequency of allelic and genotypic variants of the IL4 gene rs 1800629 polymorphism in the main and control groups

Alleles and genotypes	Number of examined alleles and genotypes				ch2	p	RR	95% CI	OR	95% CI
	Main group		Control group							
	n	%	n	%						
G	159	72.3	175	83.3	7.6	p = 0.01	0.9	0.6 - 1.26	0.5	0.33 - 0.83
C	61	27.7	35	16.7	7.6	p = 0.01	1.2	0.66 - 2.01	1.9	1.21 - 3.05
G/G	61	55.5	74	70.5	5.2	p = 0.03	0.8	0.48 - 1.3	0.5	0.3 - 0.91
G/C	37	33.6	27	25.7	1.6	p = 0.30	1.3	0.78 - 2.2	1.5	0.81 - 2.64
C/C	12	10.9	4	3.8	3.9	p = 0.05	2.9	1.54 - 5.32	3.1	1.01 - 9.44

Table 3. Differences in the frequency of allelic and genotypic variants of the rs1800629 polymorphism of the IL4 gene in the control group and in pregnant women with severe (pneumonia comilcated) COVID-19

Alleles and genotypes	Number of examined alleles and genotypes				χ^2	p	RR	95% CI	OR	95% CI
	pregnant women with severe (pneumonia comilcated) COVID-19		Control group							
	n	%	n	%						
G	101	72.1	175	83.3	6.3	p = 0.03	0.9	0.51 - 1.46	0.5	0.31 - 0.87
C	39	27.9	35	16.7	6.3	p = 0.03	1.2	0.7 - 1.91	1.9	1.16 - 3.23
G/G	37	52.9	74	70.5	5.6	p = 0.03	0.8	0.37 - 1.5	0.5	0.25 - 0.88
G/C	27	38.6	27	25.7	3.3	p = 0.10	1.5	0.74 - 3.03	1.8	0.95 - 3.46
C/C	6	8.6	4	3.8	1.8	p = 0.20	2.3	0.78 - 6.5	2.4	0.66 - 8.43

Table 4. Differences in frequency of allelic and genotypic variants of IL4 gene rs1800629 polymorphism in pregnant women mildly infected with COVID-19 and control groups

Alleles and genotypes	Number of examined alleles and genotypes				ch2	p	RR	95% CI	OR	95% CI
	Pregnant women with mild COVID-19		Control group							
	N	%	n	%						
G	58	72.5	175	83.3	4.3	p = 0.05	0.9	0.4 - 1.89	0.5	0.29 - 0.97
C	22	27.5	35	16.7	4.3	p = 0.05	1.1	0.75 - 1.76	1.9	1.04 - 3.47
G/G	24	60.0	74	70.5	1.5	p = 0.30	0.9	0.3 - 2.4	0.6	0.3 - 1.34
G/C	10	25.0	27	25.7	0.0	p = 0.95	1.0	0.29 - 3.22	1.0	0.42 - 2.23
C/C	6	15.0	4	3.8	5.6	p = 0.03	3.9	1.25 - 12.36	4.5	1.3 - 15.28

The distribution of weakened heterozygous G/C and C/C genotypes in the studied groups of patients was noted, respectively - 33.6% and 10.9%, in the control group - 25.7% and 3.8%, respectively. The frequency of the G/C heterozygous genotype is somewhat increased in the patient group compared to the control group (33.6% and 25.7%, respectively). According to statistical data, the presence of this genotype increases the risk of infection with COVID-19 by more than 1.5 times (χ^2 =1.6; P=0.30; OR=1.5; 95 % C 0.81-2.64) (Table 2).

The frequency of the attenuated homozygous C/C genotype was also significantly increased in the patient group (11.0%) compared to the control group (3.8%). According to the analysis, in the presence of this genotype, the risk of developing a viral infection increased significantly by 3.1 times (χ^2 =3.9; r =0.05; OR=3.1; 95% CI:1.01-9, 44).

According to the obtained results, the ratio of G and C alleles in pregnant women infected with Covid-19 and control groups was 83.3% and 16.7%, respectively - 72.1% and 27.9%. The frequency of homozygous G/G genotype was 52.9% and 70.5% (χ^2=5.6; P=0.03; OR=0.5; 95%CI: 0.25-3.46). Heterozygous G/C genotype was found to increase the severity of COVID-19 by 1.8 (38.6% and 25.7%, respectively; χ^2 =3.3; r=0.1; OR=1.8; 95% CI: 0.95-3.46) 3 - table.

There was a significant difference in the prevalence of the recessive C allele and the minor C/C genotype between this subgroup of pregnant women with COVID-19 and the control sample (27.9%, 16.7% and 8.6%, 3.8% respectively). According to statistical analysis, in the presence of weakened C/C genotype, the risk of disease development (pneumonia development) increases more than 2.0 times (χ^2 =1.8; r=0.20; OR=2.4; 95% CI: 0.66 - 8.43). (Table 3)

No significant differences were found when comparing the genotypic parameters of women with severe infection with COVID-19 and pregnant women mildly infected with COVID-19. But when they were compared with the control group, the difference was high. Table 4 shows the results of IL4 rs1800629 gene in pregnant women mildly infected with COVID-19 and control groups. In it, the G and C alleles were 83.3% and 16.7% in patients and controls, respectively, compared to 72.3% and 27.7%. The frequency of G/G, G/C and C/C genotypes was found to be 70.5%, 25.7% and 3.8% compared to 60.0%, 25.0% and 15.0% respectively.

Notably, according to statistics, C/C the frequency of the genotype is higher in the group of women mildly infected with COVID-19 (15.0%) than in the control group (3.8%). According to statistical results, IL4 with this genotype the risk of disease development in gene carriers increases significantly by 4.5 times (χ^2 =5.6; r =0.03; OR=4.5; 95%CI: 1.3-15.28). The frequency of homozygous G/G genotype was lower in patients than in controls (60.0% vs. 70.5%, respectively, $\chi 2$ =1.5; r =3.0; OR=0.6; 95%CI: 0,3-1,34), This shows the protective effect of the genotype on the aggravation of the disease and the development of complications.

It should be noted that when comparing the frequency distribution of alleles and genotypes of this locus in pregnant women mildly infected with COVID-19, we found significant differences from healthy people (p>0.05) (Table 4).

Interestingly, the C/C genotype rs1800629 polymorphism of the IL4 gene was reported to be associated with progression to severe form of COVID-19 when analyzed together with the development of the coronavirus disease and clinical outcomes. This genotypic variant is more common in women with severe COVID-19. With this weakened C/C genotype, the probability of developing a viral infection increases more than 3.0 times with other genotypic variants (χ^2 = 3.9 and p=0.05; 95%CI: 1.01 - 9.44).

Analyzing the literature, we found information explaining the role of the IL4 gene in the pathogenesis of the development and exacerbation of COVID-19, depending on the involvement of IL4 in the immune system [17]. However, there is no clear information about the rs1800629 polymorphism and the development of pneumonia. But taking into account the involvement of the wave of cytokines in the immune system and the inflammatory process, we can say that the development of ARDS in patients infected with coronavirus is directly related to this gene polymorphism.

In our research, we found a significant association of the rs1800629 polymorphism of the IL4 gene with the risk of disease exacerbation in the Uzbek population, compared with pregnant women infected with COVID-19 and conditionally healthy people. Given the paucity of literature and data on the pathogenesis of COVID-19, the prevalence of genotypic variants of this polymorphic locus and its contribution to the development of different nosologies associated with cytokine imbalance vary in different populations and nations. According to our results, the rs1800629 polymorphism of the IL4 gene is associated with the weakening of the immune system and the development of the inflammatory process in our population, with the pathogenesis of the complications and severity of the coronavirus disease.

5. Summary

Our results allow us to conclude that the attenuated homozygous C/C genotype of the IL4 gene plays an important role in the pathogenesis of the development of COVID-19. The presence of this genotype causes the weakening of the immune system in the body and taking into account the role of the cytokine storm in the development of the pathogenesis of COVID-19, the C/C genotypic variant of the IL4 gene causes a 3-fold increase in the risk of infection and complications from COVID-19. The homozygous G/G genotype illustrates a protective effect.

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