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COMPARATIVE ANALYSIS OF THE FREQUENCY OF RS1801394 POLYMORPHISM (GENE LOCALIZATION ON CHROMOSOME 5P15.31) 66A> G IN THE MTR GENE IN THE GROUP OF PATIENTS WITH POSTCOVID COMPLICATIONS OF THE MAXILLOFACIAL AREA

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Abstract

In the article of genetic studies of patients with post-covid maxillofacial complications. The condition after COVID-19 is considered a life-threatening disease, ranging from mild symptoms to serious complications. Candidiasis is the most common type of superficial purulent infection. The Candida species is a frequent inhabitant of the oral mucosa, but its growth is inhibited by other organisms in the body, which prevents any pathological change in the mucous membrane of this fungus. Candida albicans is the most common yeast, followed by Candida glabrata, Candida krusei, Candida tropicalis and Candida stellatoidea. According to this systematic review, 57 cases of oral candidiasis and one case of retinitis candidiasis were reported in patients undergoing treatment for COVID-19. Single-cell RNA-seq analysis of angiotensin-converting enzyme II (ACE2) expression and serologic examination of samples indicates that ACE2 may be the cellular receptor for SARS-CoV-2, suggesting that ACE2-expressing cells are likely to be the main target cell type that vulnerable to SARS-CoV-2 infection. As a rule, there is a high expression of ACE2 r on the epithelial cells of the oral mucosa, enrichment is enriched in epithelial cells of the tongue. There were few reports prior to this study.

Keywords: post-covid maxillofacial complications, COVID-19, oral mucosa, allele.

Introduction.

The post-COVID-19 condition is considered a life-threatening illness, ranging from mild symptoms to serious complications [1-4]. COVID-19 has now been declared a multi-organ disease with a wide range of manifestations [2]. The pathogen that caused the pandemic is Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2), which caused a global medical crisis and drained health resources [6].

The main problems with the Covid-19 pandemic are that the symptoms of the disease are varied and appear in different patients [9]. Some develop severe symptoms, others asymptomatic. In severe cases, a typical picture is observed [5]. Most symptoms appear about 2-14 days after exposure to the virus, including fever, muscle pain, headache, cough, sore throat, loss of taste or smell [7-10]. In severe cases, there is severe lung infection, breathing difficulties due to pneumonia, and the development of ARDS, which can be fatal in 40% of patients [4]. It can progress to the terminal stage of multiple organ failure. This can cause neurodegenerative changes, neurological deficits and damage to the BBB. Patients may present with anxiety, impaired attention, memory impairment, depressed mood, and PTSD.

The current situation of the researchers shows that the coronavirus enters human cells through the angiotensin-converting enzyme receptor 2 (ACE2) via scRNAseq, observed when analyzing the data. Researchers have identified several organs at increased risk of injury and susceptibility to SARSCoV2 [11].

Thus, organs with abundant distribution of ACE2 receptors can become viral host cells, causing inflammation in associated tissues such as the tongue and salivary glands. Intraoral signs and symptoms associated with COVID-19 include taste changes, recurrent mouth ulcers, desquamative gingivitis, petechiae, and concomitant infections such as the growth of a fungus called candidiasis [12-14].

Osteomyelitis is an inflammation of the cortex and bone marrow that usually occurs on the chin after a chronic infection [13]. Local conditions that negatively affect blood supply or cause tissue necrosis can also render the host susceptible to bone infections or local osteomyelitis [10]. Osteomyelitis is diagnosed based on the patient's medical history, clinical examination, and the results of surgical and X-ray examination. Histopathological examination may be consistent with the diagnosis, and microbiological examination is also helpful [15].

Osteomyelitis has a number of clinical manifestations that depend on the virulence of the infectious organism, the resistance of the host and the response of the periosteum to inflammation [16].

There are few reports in the literature on osteomyelitis of the mandible after conventional dental treatment [17].

Since the prevalence of clinical complications is not yet sufficiently understood and is not known, the spectrum of manifestations of COVID-19 in the oral cavity can be very wide and manifest in different ways [12]. The purpose of this case is to study about a defect in the soft tissues of the face and oral cavity, which can be a consequence of infection with COVID-19.

Material and methods. From 2020 to 2021, we carried out a comprehensive examination and treatment of 118 patients with COVID-19 and its purulent-necrotic complications in the maxillofacial area, who were being treated at the post-COVID center of the Multidisciplinary Clinic of the Tashkent Medical Academy.

Molecular genetic studies were performed in the Hematology Department of the TMA Multidisciplinary Clinic.

This part of the work consisted of several stages:

1. Blood sampling (Figure 1).
2. Isolation of DNA from peripheral blood lymphocytes.
3. Carrying out PCR.
4. Carrying out electrophoresis and visualization of results.

Figure 1. Blood sampling

In the course of the work, 4 polymorphic variants of genes were investigated (table 1).

Table 1

List of studied gene polymorphisms

Gene (abbreviation)	Localization	Polymorphism	A source
MTHFR	1p36.22, 677 C>T	rs1801133	Morrison N.A. et all. 1992
MTHFR	1p36.22, 1298 A>C	rs1801131	Braun N. et all 1996
MTR	1q43, 2756 A>G	rs1805087	Um J.Y., et all. 2004; 50: 647-650.40
MTR	5p15.31, 66 A>G	rs1801394	Vincenti V. et all. 1996

Results and discussion. The study of the frequencies of detection of alleles and genotypes of polymorphism 66A> G rs1801394 in the MTR gene showed the presence of differences in their distribution between 1-2 and control groups (Table 2).

Table 2

Frequency of distribution of alleles and genotypes of rs1801394 polymorphism (gene localization on chromosome 5p15.31) 66A> G in the MTR gene in patient and control groups

Num	Groups	Allele frequency				Genotype distribution frequency					
		A		G		A /A		A / G		G/ G	
		n	%	n	%	n	%	n	%	n	%
1	Main group (n = 70)	75	53,57	65	46,43	10	14,29	36	51,43	24	34,29
2	Control group (n = 41)	73	89,02	9	10,98	32	78,05	7	17,07	2	4,88

During the study, it was possible to establish the frequency of detection of the A allele, which was 1.15 times higher than the frequency of detection of the G allele in group 1, and 8.1 times in the control group. Genotype A / A in group 1, in comparison with genotypes A / G and G / G, was detected less often 6.99 times, respectively, in the population sample 4.57 times more often (Table 2).

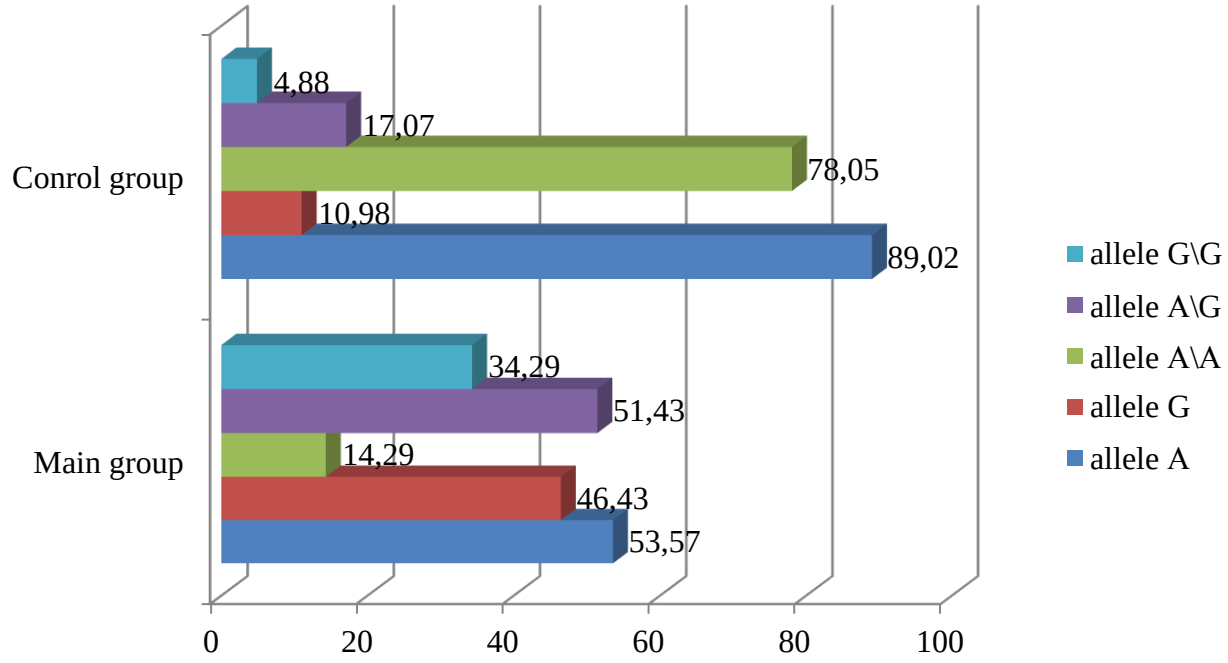

Diagram. 4.3. Frequency of distribution of alleles and genotypes rs1801394 (gene localization on chromosome 5p15.31) 66A> G in the MTR gene in patient and control groups

The results of a comparative analysis of the frequencies of detection of alleles and genotypes of polymorphism 66A> G rs1801394 in the MTR gene of group 1 and in the population, sample are presented in Table 3

Table 3

Differences in the frequency of allelic and genotypic variants of the rs1801394 polymorphism (Localization of the gene on chromosome 5p15.31) 66A> G in the MTR gene in patient groups

Alleles and genotypes	Number of examined alleles and genotypes				Xi2	p	RR	95%CI	OR	95%CI
	Main group		Control group							
	n	%	n	%						
A	75	53,57	73	89,02	29,25	0,00	0,60	0,423 - 0,857	0,14	0,07 - 0,288
G	65	46,43	9	10,98	29,25	0,00	1,66	0,48 - 5,754	7,03	3,467 - 14,253
A /A	10	14,29	32	78,05	44,694	0,001	0,183	0,062 - 0,536	0,047	0,019 - 0,115
A / G	36	51,43	7	17,07	12,859	0,001	3,012	1,768 - 5,131	5,143	2,101 - 12,588
G/ G	24	34,29	2	4,88	12,466	0,001	7,029	4,523 - 10,924	10,174	2,807 - 36,879

As can be seen from table 4.8, in the control group, the prevalence of allele A was noted compared to allele G, the frequencies of which were 89.02% versus 10.98%, respectively. In the main group, the frequency of the A allele, which was 53.57%, also prevailed, compared with the frequency of the G allele, which was 46.43%. In general, the severity of differences was at a high level in practically healthy individuals, there is a pronounced difference between alleles A and G in patients with postcoid complications of MFA was 1.15 ($\chi2$ = 29.25; p = 0.00; RR = 0.60; OR = 0.14; 95% CI: 0.423 - 0.857). It was also noted a more significant, statistically significant, 4.22 times, excess of the frequency of genotype G, among patients with postcoid complications of MCL, relative to the frequency of detection of this genotype in the control. The frequency of detection of genotype A / G polymorphism was revealed more than 3.01 times, it prevailed in group 1, relative to its values in the control group ($\chi2$ = 12.859; p = 0.001; RR = 3.012; OR = 5.143; 95% CI: 1.768 - 5.131). The frequency of occurrence of the G / G genotype differed among patients with postcoid complications of MFA exceeding 7.02 times, in the control group among conventionally healthy individuals, amounting to 34.29 and 4.88%, respectively ($\chi2$ = 12.466; p = 0.001; RR = 7.029 ; OR = 10.174; 95% CI: 4.523 - 10.924).

Thus, we have found that in patients with postcoid complications of the MFA, the unfavorable G allele of the 66A> G rs1801394 polymorphism in the MTR gene is more common than in healthy individuals. There is a high frequency of occurrence of this allele with a predominance of the homozygous variant G / G (from 2.3 to 7.02 times). At the same time, the differences between group 1 and the control sample were noted at the level of the trend, and the trend had a borderline level of statistical significance. These data allow us to conclude that the G allele and the G / G genotype of the 66A> G rs1801394 polymorphism in the MTR gene have a predisposing effect on the risk of development and severe clinical course of postcoid complications of

MCL. Since this polymorphism is located in the promoter region of the gene and refers to functional polymorphisms. The presence of the G allele in patients with postcoid complications of the MFA is accompanied by a decrease in the production of the MTR gene in the presence of the G / G genotype. The pattern of the inflammatory response gene is capable of modifying the implementation of the immune and inflammatory response in the direction of an inadequate hyperinflammatory response, leading to the progression and development of a more severe form of postcoid complications of MCL.

Conclusion:

Thus, our data confirm the complexity of the genetic mechanism for the development of polyposis processes in patients with postcoid complications of PCO and indicate the need and importance of understanding complex gene interactions in the analysis of the development and clinical stage of the studied pathology. Analyzing the prevalence of genotypic variants of this polymorphism, we revealed a direct association of the T / T monogenotype of the 677C> T rs1801133 polymorphism in the MTHFR gene, the C / C monogenotype of the 66A> G rs1801394 polymorphism in the MTR gene with the development of postcoid complications of the PLC.

Our results confirm the hypothesis that the presence of an unfavorable genotypic variant of the MTHFR and MTR gene can lead to a violation of the synthesis (expression) in the conversion of homocysteine to methionine in the presence of cofactors - pyridoxine (vitamin B6) and cyanocobalamin (vitamin B12) - and the substrate - folic acid and causes a reduced resistance of the vessels of the body, the activity of the enzyme may decrease as a result of nucleotide substitutions in the gene encoding it. As a result, the metabolic pathway of homocysteine conversion is disrupted and its content in the blood plasma increases, and leads to an increase in the risk of postcoid complications of MCL.

The absence of significant differences in the prevalence of genotypes of genes 2756A> G in the MTR gene and 1298 A> C in the MTHFR gene among conditionally healthy donors and patients with postcoid complications of MFA may be explained by the fact that the presence of unfavorable polymorphism, in itself, is still insufficient for the development of this disease. In genetically predisposed persons, postcoid complications of the MFA will develop according to the interaction scheme in the "genotype-phenotype" system (genetic-environmental). Moreover, the presence of unfavorable genotypic variants can affect the clinical course of the disease.

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