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**IMMUNOGENETIC CHARACTERISTICS OF COVID-19 IN THE REPUBLIC OF
KARAKALPAKSTAN**

Janibekov J.J.¹

¹Qoraqalpog'iston tibbiyot instituti.



Janibekov J.J. Tibbiyot fanlari nomzodi, Qoraqalpog'iston tibbiyot institutining "Yuqumli kasalliklar, va dermatovenerologiya" kafedrası mudiri.

ORCID: <https://orcid.org/0009-0009-5223-1429>

E-mail: janibekov3001@gmail.com tel: +998906541654

Abstract

The clinical course and outcomes of COVID-19 are significantly modulated by host immunogenetic factors, particularly human leukocyte antigen (HLA) gene polymorphisms and cytokine gene variations. Regional immunogenetic profiling is essential for identifying ethnic-specific genetic susceptibility and protective mechanisms against severe SARS-CoV-2 infection. To investigate the immunogenetic characteristics, HLA allele frequency distribution, and cytokine gene polymorphisms in patients with COVID-19 in the Republic of Karakalpakstan, and to establish their association with disease severity and clinical outcomes.

Key words: SARS-CoV-2, immunogenetic features, Karakalpakstan, MTHFR gene, TNF gene, IL-6 gene, cytokine storm.

**ИММУНОГЕНЕТИЧЕСКИЕ ОСОБЕННОСТИ COVID-19 В РЕСПУБЛИКЕ
КАРАКАЛПАКСТАН**

Жанибеков Жанабай Жумабаевич

janibekov3001@gmail.com

<https://orcid.org/0009-0009-5223-1429>

Аннотация

Клиническое течение и исходы COVID-19 в значительной степени модулируются иммуногенетическими факторами хозяина, в частности полиморфизмом генов человеческого лейкоцитарного антигена (HLA) и вариациями генов цитокинов. Региональное иммуногенетическое профилирование имеет решающее значение для выявления этноспецифической генетической предрасположенности и защитных механизмов против тяжелой формы инфекции SARS-CoV-2. Целью исследования являлось изучение иммуногенетических характеристик, распределения частот аллелей HLA и полиморфизма генов цитокинов у пациентов с COVID-19 в Республике Каракалпакстан, а также установление их связи с тяжестью заболевания и клиническими исходами.



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Ключевые слова: SARS-CoV-2, иммуногенетические особенности, Каракалпакстан, ген MTHFR, ген TNF, ген IL-6, цитокиновый шторм.

ҚОРАҚАЛПОҒИСТОН РЕСПУБЛИКАСИДА COVID-19 НИНГ ИММУНОГЕНЕТИК ХУСУСИЯТЛАРИ

Жанибеков Жанабай Жумабаевич

janibekov3001@gmail.com

<https://orcid.org/0009-0009-5223-1429>

Аннотация

COVID-19 нинг клини кечиши ва оқибатлари эгасининг иммуногенетик омиллари, хусусан, одам лейкоцитар антигени (HLA) генлари полиморфизми ва цитокин генларининг ўзгарувчанлиги билан сезиларли даражада бошқарилади. Минтакавий иммуногенетик профилни аниқлаш оғир кечувчи SARS-CoV-2 инфекциясига қарши этник жиҳатдан хос бўлган генетик мойиллик ва ҳимоя механизмларини аниқлашда муҳим аҳамиятга эга. Тадқиқотнинг мақсади Қарақалпоғистон Республикасидаги COVID-19 билан оғриган беморларда иммуногенетик хусусиятларни, HLA аллеллари тезлигининг тарқалишини ва цитокин генлари полиморфизмини ўрганиш ҳамда уларнинг касаллик оғирлиги ва клинко-патологик оқибатлари билан боғлиқлигини аниқлашдан иборат.

Калит сўзлар: SARS-CoV-2, иммуногенетик хусусиятлар, Қарақалпоғистон, MTHFR гени, TNF гени, IL-6 гени, цитокин бўрони.

Introduction

The global pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) highlighted dramatic inter-individual variations in clinical presentation, ranging from asymptomatic infection to fatal acute respiratory distress syndrome (ARDS) and systemic hyperinflammation. While classical risk factors such as age, metabolic comorbidities, and cardiovascular disease contribute to adverse outcomes, accumulating immunogenetic evidence demonstrates that host genetic architecture specifically human leukocyte antigen (HLA) gene polymorphisms and cytokine single nucleotide polymorphisms (SNPs) plays a fundamental role in determining susceptibility, immune response magnitude, and disease progression. Host immune responses are heavily governed by the major histocompatibility complex (MHC/HLA), which encodes surface glycoproteins essential for presenting viral peptide antigens to T lymphocytes. Differences in HLA class I (HLA-A, HLA-B) and class II (HLA-DRB1) allele binding affinities directly dictate the efficiency of early cytotoxic T-cell activation and viral clearance, thereby influencing whether an infection remains mild or progresses to severe pulmonary damage.

In addition to antigen presentation, the host's genetically predetermined capacity for cytokine production regulates the intensity of the systemic inflammatory response. Genetically driven hyperactivation of pro-inflammatory pathways often referred to as a "cytokine storm" is a hallmark of severe COVID-19. Functional polymorphisms within promoter regions of key inflammatory genes, such as interleukin-6 (IL-6 -174 G/C), tumor necrosis factor-alpha (TNF- α -308 G/A), and interleukin-10 (IL-10-1082 A/G), modulate baseline transcript levels and systemic secretion rates. Alleles associated with high cytokine expression exacerbate microvascular endothelial disruption, excessive neutrophil recruitment, and systemic oxidative stress. Because the distribution of HLA alleles and cytokine gene variants varies substantially across global ethnicities due to ancestral evolutionary pressures, population-specific immunogenetic profiling is critical for understanding regional disease dynamics.



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Despite extensive global research, the immunogenetic landscape of COVID-19 within distinct ethnic populations of Central Asia, particularly in the Republic of Karakalpakstan, remains understudied. The Karakalpak population possesses unique genetic structures shaped by historical gene flow and geographic isolation, which may confer specific immunogenetic risk or protective profiles against viral pathogens. Investigating regional HLA allele frequencies and cytokine gene variants is essential for elucidating the molecular mechanisms driving severe COVID-19 outcomes in this region. Therefore, this study aimed to investigate the immunogenetic characteristics of COVID-19 in the Republic of Karakalpakstan by evaluating the distribution of HLA class I and II alleles alongside key cytokine gene polymorphisms, correlating these immunogenetic markers with clinical severity to establish population-specific biomarkers for early risk stratification and targeted clinical management.

Material and methods

This clinical investigation was conducted at the Bukhara Regional Infectious Diseases Hospital between 2020 and 2022 to examine the immunogenetic and clinical characteristics of patients with COVID-19. The study cohort comprised 140 participants, including 120 hospitalized patients with confirmed SARS-CoV-2 infection and 20 healthy individuals who served as the control group. The diagnostic confirmation of COVID-19 was established through comprehensive pulmonological evaluations, epidemiological history, clinical presentation, and specific laboratory assays. The control group was age- and sex-matched to the patient cohort, with a comparison group selected via randomized sampling under strict inclusion criteria: patients under 65 years of age, admitted within 10 days of symptom onset, and free of major severe chronic comorbidities.

Clinical diagnoses and disease severity stratification strictly adhered to the methodological guidelines outlined in the temporary recommendations for the management of COVID-19 (8th edition), approved by Order No. 82 of the Ministry of Health of the Republic of Uzbekistan on April 21, 2021. Based on these national diagnostic criteria, infected patients were categorized into two distinct clinical presentation variants. Primary clinical evaluation focused on characteristic manifestation patterns, including general intoxication symptoms (headache, myalgia, sleep disturbances, anorexia, nausea, and vomiting), lower respiratory signs (cough with difficult expectoration, dyspnea at rest or upon mild exertion), altered levels of consciousness, and confirmed laboratory derangements upon admission.

Statistical analysis of the clinical and laboratory data was performed using variation statistics methodologies. For quantitative continuous variables, the arithmetic mean (M) and standard error of the mean were calculated, whereas categorical parameters were expressed as relative frequencies (percentages, %). Inter-group comparisons and statistical significance were determined using Student's t-test, with error probability (p) evaluated across four established significance thresholds: high ($p < 0.001$), moderate ($p < 0.010$), low ($p < 0.050$), and statistically non-significant ($p > 0.050$).

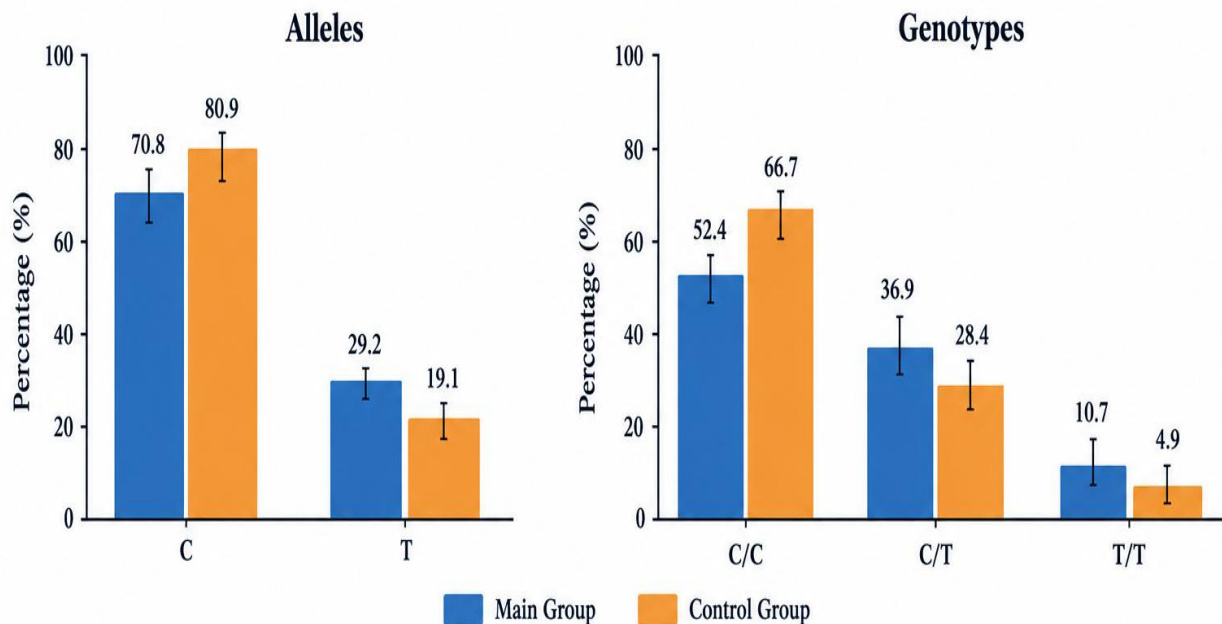
Results

Statistically significant differences in the manifestation of COVID-19 were identified among the population of Karakalpakstan districts and Nukus city. Patients from the districts most often exhibited severe or extremely severe forms of the disease, wave-like course, signs of pneumonia with "CT-3" type lung damage (50-75%), grade 3 respiratory failure, and received therapy with ventilator support according to indications. In both groups, the main symptoms of COVID-19 were fatigue, headache, dry cough, shortness of breath, sore throat, and anosmia. However, in patients from the regions, compared to the comparison group, shortness of breath due to air hunger, wet cough, runny nose, sore throat, and diarrhea were more frequently recorded, confirming the impact on various parts of the respiratory and gastrointestinal tracts due to severe disease course. At the same time, patients did not complain of severe fatigue, which is considered to be associated with less pronounced cytokine storm cases in this group. Among complications in patients from the districts, thromboses

were more common, while liver failure and hyperglycemia were less frequently identified, confirming the presence of specific characteristics of disease course depending on the region. Regarding concomitant pathology, the compared groups by region were generally comparable, but the frequency of stage 3 hypertension and chronic cholecystitis was statistically significantly lower among the population of Karakalpakstan regions. At the same time, recovery from the disease was significantly more frequently recorded among patients in Nukus city.

As can be seen from Table 1, the analysis results showed statistically significant differences between the main group of examined patients and the control group, as well as compared to the group of patients with moderate severity. In the main group of patients with COVID-19, the frequency of occurrence of the C allele was found to be significantly lower compared to the control group indicators ($OR \geq 0.6$), while the T allele, conversely, was a negative marker in this subgroup with $OR \geq 1.7$ ($\chi^2 = 4.5$, $p = 0.05$). The differences in the frequency of occurrence of C/C, C/T, and T/T genotypic combinations of the C677T polymorphism in the MTHFR gene in this sample were not of reliable significance.

The C677T polymorphism in the MTHFR gene was examined when comparing the group of patients with moderate severity with the control group (Table 5.2.47). The frequency of occurrence of the C allele was also significantly lower compared to the control group, as in the general group ($OR \geq 0.5$), while the T allele, conversely, was a negative marker in this subgroup with $OR \geq 2.0$ ($\chi^2 = 5.6$, $p = 0.03$). The differences in the frequency of occurrence of C/T and T/T genotypic combinations of the C677T polymorphism in the MTHFR gene in this sample were not of real significance, while the C/C protector genotype in the studied subgroup was of real significance ($\chi^2 = 5.4$, $p = 0.03$, $OR \geq 0.4$).



1 Figure. Distribution of alleles and genotypes in the main and control groups

We continue to examine the differences in the frequency of occurrence of allelic and genotypic variants of the C677T polymorphism in the MTHFR gene in patients with moderately severe disease course in the main group compared to the group with severe disease course. In the group of severe patients compared with the control group, no significant differences were found in either alleles or genotypic distribution.



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Conclusion

By 2023, the epidemiological trajectory of COVID-19 in the Republic of Karakalpakstan demonstrated clear stabilization and a progressive decline in overall morbidity rates. Nevertheless, the disease disproportionately impacts working-age individuals (31-54 years), alongside a gradual shift toward older patient demographics. The regional administrative center, Nukus city, remains the primary focal point for SARS-CoV-2 transmission, highlighting the ongoing necessity for targeted preventative measures, enhanced vaccination coverage, and sustained population-level immunity.

Immunogenetic and molecular risk stratification revealed distinct population- and territory-specific genetic susceptibility patterns across Karakalpakstan. Among rural populations, the G/A genotype of the G4682A polymorphism within the TNF gene emerged as a significant negative prognostic marker associated with severe COVID-19 progression compared to urban residents of Nukus. Conversely, the C allele of the G174C polymorphic variant in the IL-6 gene was significantly enriched in Nukus patients with severe disease, whereas the G allele and heterozygous G/C genotype demonstrated protective value. Additionally, the T allele variant of the C677T polymorphism in the MTHFR gene was strongly characteristic of a moderately severe clinical course. These findings confirm that regional immunogenetic profiling enables high-precision risk stratification, guiding personalized therapeutic interventions and targeted public health strategies across distinct urban and rural populations.

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