UDC 616.98:578.834COV]-06-02:575.174.015.3
DOI: 10.14739/2310-1210.2024.5.307248

A modern view on the role of single nucleotide polymorphism of human genes in the formation of unfavorable consequences of the new coronavirus disease (COVID-19)

Yu. Yu. Riabokon*[1,A,E,F], E. M. Huseynov[2,B,C,D], K. V. Kalashnyk[1,B,C,E]

[1]Zaporizhzhia State Medical and Pharmaceutical University, Ukraine, [2]Azerbaijan Medical University, Baku

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim – to analyze the current literature on the role of single nucleotide polymorphism (SNP) of human genes in shaping the clinical course of the new coronavirus disease (COVID-19).

Results. Based on the results of the analysis and synthesis of the current literature on the role of SNP in shaping the clinical course and outcome of COVID-19, the clinical and prognostic significance of SNP of genes encoding receptors responsible for the penetration of SARS-CoV-2 into target cells has been demonstrated. The presence of the D-allele of the ACE gene (DD and ID genotypes) is associated with the highest risk of severe COVID-19, which makes it possible to offer it as an informative prognostic marker of COVID-19 severity. SNP of the TMPRSS2 co-receptor gene, known as the androgen responsive gene, at certain loci is prognostically important, as it leads to an increase in TMPRSS2 expression in men, which promotes virus fusion with the target cell membrane and has an unfavorable effect on the course of COVID-19 in men.

The data accumulated in the current literature on the clinical and prognostic value of SNP host genes encoding the immune response has also been analyzed. The role of HLA SNP genes, genes encoding innate immunity factors (TLR), as well as genes encoding pro-inflammatory cytokines (IL-6, TNF-α, etc.) and acute-phase inflammatory components (CRP) in the development of severe COVID-19 and the risk of death has been demonstrated. Attention has been paid to the determined role of SNP in the ACE gene in the development of pulmonary embolism in patients with severe COVID-19. The article has analyzed publications on the SNP role of host genes in the development of clinical events that are currently interpreted as long COVID. The prognostic role of the IL-10 gene SNP and its receptor gene in the formation of long-term consequences of the new coronavirus infection has been demonstrated.

Conclusions. SNP of host genes encoding receptors responsible for the entry of SARS-CoV-2 into target cells and SNP of genes encoding immune response have some prognostic value in assessing the risk of severe course and adverse effects of COVID-19. The accumulation of data on genetic risk factors for adverse outcomes of the new coronavirus disease will allow us to enhance the understanding of this infection pathogenesis, improve patient stratification and individualize therapeutic interventions.

Keywords: coronavirus disease, COVID-19, viral infection, single nucleotide polymorphism, clinic, diagnosis, prognosis.

Zaporozhye Medical Journal. 2024;26(5):411-416

***E-mail:** ryabokonzsmu@gmail.com

Сучасний погляд на роль однонуклеотидного поліморфізму генів людини у формуванні особливостей клінічного перебігу та наслідків нової коронавірусної хвороби (COVID-19)

Ю. Ю. Рябоконь, Е. М. Гусейнов, К. В. Калашник

Мета роботи – проаналізувати відомості сучасної наукової літератури щодо ролі однонуклеотидного поліморфізму (ОП) генів людини у формуванні особливостей клінічного перебігу нової коронавірусної хвороби (COVID-19).

Результати. У результаті аналізу й узагальнення відомостей фахової літератури щодо ролі ОП генів господаря у формуванні особливостей клінічного перебігу та наслідків COVID-19 показано клініко-прогностичне значення ОП генів, що кодують рецептори, відповідальні за потрапляння SARS-CoV-2 до клітин-мішеней. Якщо виявлено D-алель гена ACE (генотипи DD і ID), ризик розвитку тяжкого перебігу COVID-19 найвищий. Отже, є підстави визначити його як інформативний прогностичний маркер тяжкості COVID-19. ОП гена ко-рецептора TMPRSS2, відомий як андрогенний реактивний ген, у певних локусах має прогностичне значення, оскільки призводить до збільшення експресії TMPRSS2 у чоловіків, а отже спричиняє злиття вірусу з мембраною клітини-мішені та, відповідно, має несприятливий вплив на перебіг COVID-19 саме в чоловіків. Проаналізовано також відомості наукової літератури щодо клініко-прогностичного значення ОП генів господаря, що кодують імунну відповідь. Показано роль ОП генів системи HLA, генів, що кодують фактори вродженого імунітету (TLR), а також генів, які кодують прозапальні цитокіни (IL-6, TNF-α тощо) та гострофазові компоненти запалення (CRP) у розвитку тяжкого перебігу COVID-19 та ризику летального наслідку. Описано роль ОП поліморфізму гена ACE у розвитку тромбоемболії легеневої артерії у хворих із тяжким перебігом COVID-19. Вивчили дані щодо ролі ОП генів господаря в розвитку клінічних подій, що визначають нині як long-COVID. Описано прогностичну роль ОП гена IL-10 та гена його рецептора в формуванні віддалених наслідків нової коронавірусної інфекції.

Висновки. ОП генів господаря, що кодують рецептори, відповідальні за проникнення SARS-CoV-2 у клітини-мішені, а ОП генів, що кодують імунну відповідь, мають певне прогностичне значення щодо оцінювання ризику тяжкого перебігу та несприятливих наслідків COVID-19. Накопичення відомостей про генетичні фактори ризику несприятливого перебігу нової коронавірусної хвороби дасть змогу поглибити розуміння патогенезу цієї інфекції, сприятиме покращенню стратифікації хворих та індивідуалізації терапевтичного втручання.

Ключові слова: коронавірусна хвороба, COVID-19, вірусна інфекція, однонуклеотидний поліморфізм, клініка, діагностика, прогноз.

Запорізький медичний журнал. 2024. Т. 26, № 5(146). С. 411-416

It is known that the cellular component of immune defense plays a key role in the pathogenesis of infectious diseases of viral origin. One of the properties of the body's immune system is a significant variation in resistance to various infectious diseases. Each person has an individual set of nucleotide pairs, which determines the reactivity of innate and acquired immunity and predisposes to resistance or susceptibility to various pathological conditions [1,2,3]. Today, it is important to study the role of the various human gene activity in the course of diseases and complication development. Studies of many scientists have shown that the activity of cytokine production depends on the polymorphism of the genes that encode them [4,5].

For molecular diagnostics of diseases, the most important change in gene structure is single nucleotide polymorphism (SNP), which determines the peculiarities of the defense reaction development and the state of the body immunological reactivity. Many researchers point out the role of cytokine gene SNP in predicting the occurrence and severity of infectious diseases, and in some clinical situations, it is even important for individualizing therapy [6,7].

The significant variability in the clinical symptoms of coronavirus disease (COVID-19) is currently explained by both viral factors, which include the virus strain and viral load, and the peculiarities of the immune response to SARS-CoV-2 replication in each patient, which is associated with genetic factors [8,9]. Given the leading role of immune-dependent mechanisms in the progression of the new coronavirus disease, it is particularly important to understand the role of genetic factors that determine the specificity of the receptor apparatus of host target cells and the course of the immune response to virus-infected cells.

Therefore, among the many human factors that can explain increased susceptibility to SARS-CoV-2 and a high risk of severe and fatal COVID-19, human genetic characteristics are increasingly recognized as a critical determinant of susceptibility or resistance to this infection, as well as a prognostic marker for probable clinical outcomes in infected individuals [10].

Aim

To analyze the current literature on the role of single nucleotide polymorphism of human genes in shaping the clinical course of the new coronavirus disease 2019.

Results

Today, it is clearly understood that a feature of the new COVID-19 is a great variation in clinical symptoms from almost asymptomatic to extremely severe forms [11]. To date, no specific SARS-CoV-2 mutations have been identified that could explain this difference in clinical manifestations of the disease. Therefore, there is a growing focus on clarifying the role of human genetic factors in the course of COVID-19 [11,12]. It is believed that the identification of genes associated with the severity of COVID-19 will allow to identify the main molecular pathways involved and select candidate genes for future research and therapeutic development [11,12,13].

Clinical and prognostic significance of receptor gene SNP responsible for SARS-CoV-2 entry into target cells. At the first stages of studying the pathogenesis of COVID-19, attention was drawn to host genetic factors associated with receptors through which SARS-CoV-2 is able to enter the target cell, such as polymorphisms in the genes for angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) [14].

ACE2 spans 39.98 kb of genomic DNA on chromosome Xp22, so it was immediately believed that X-linked heterozygous alleles may have a protective effect by counteracting viral infection and reducing local inflammation and, accordingly, protecting women more from the adverse effects of COVID-19 [14]. Since the ACE ID gene polymorphism is associated with diabetes mellitus, chronic heart failure, and hypertension [15], which are risk factors for adverse COVID-19 outcomes, it is currently suggested that the D-allele of the ACE polymorphism may influence the COVID-19 progression, which requires further study [14]. In addition, given that the DD genotype of the ACE gene is more common in the European population, it may to some extent explain the highest morbidity and mortality among Europeans [16,17]. A strong correlation between mortality from COVID-19 in patients with the DD genotype and ACE ID gene has been reported by other researchers [18], who believe that this genotype may also be an informative prognostic marker of the new coronavirus disease severity.

The role of ACE2 gene SNP in susceptibility to SARS-CoV-2 has been demonstrated in several studies [19,20]. SNPs of the ACE2 gene K26R (rs4646116), M82I (rs267606406) and E329G (rs143936283) have been shown to be associated with higher affinity in interaction with the S-protein of SARS-CoV-2, which leads to a more severe course of coronavirus disease [19]. At the same time, the ACE2 gene SNPs I21T (rs1244687367), E37K (rs146676783) and D355N (rs961360700) are associated with lower affinity for interaction with the S-protein of SARS-CoV-2, which may contribute to a decrease in susceptibility to this disease [19]. According to [20], a higher incidence of infection and risk of death from COVID-19 is associated with the presence the ACE2 SNP rs2285666.

The accumulated data on the SNP role of the ACE gene in susceptibility to coronavirus disease (COVID-19) and the severity of the clinical course have been summarized in a meta-analysis and evidence of certain genetic determinants of COVID-19 that exist today has been presented. The meta-analysis has shown that high susceptibility to COVID-19 was associated with the ACE gene ID genotype at the rs4646994 and rs1799752 loci, and SNP of the ACE2 gene at the rs2285666, rs2106809, and rs2074192 loci had a statistically significant association with the development of severe and critical COVID-19 [20].

However, the penetration of SARS-CoV-2 into the target cell is possible only if there is a co-receptor, the role of which is played by transmembrane serine protease (TMPRSS2), which promotes the fusion of the viral membrane with the target cell membrane and the virus entry into the cytoplasm [21,22]. TMPRSS2 is known as an androgen receptor gene, the polymorphism of which at the loci rs2070788, rs7364083, rs9974589, rs8134378 has a certain prognostic value. For example, SNP of the TMPRSS2 gene rs8134378 has been shown to increase TMPRSS2 expression in men,

which promotes virus fusion with the target cell membrane and, accordingly, has an adverse effect on the course of COVID-19 in men [23]. The genomic region of the quantitative trait locus (eQTL) expression includes not only the TMPRSS2 gene itself, but also the MX1 gene, which encodes a protein involved in cellular antiviral defense. The eQTL rs35074065 variant associated with overexpression of the TMPRSS2 co-receptor in combination with low expression of MX1 may lead to increased susceptibility to viral infection coupled with impaired cellular antiviral response. This may explain the more severe course of COVID-19 in patients with the relevant features of this genomic locus [22]. Given the important role of the TMPRSS2 gene in the initial stage of SARS-CoV-2 infection, researchers [24] suggested that targeting the expression or activity of TMPRSS2 could be a potential target for the development of antiviral drugs effective against COVID-19.

In determining the clinical and prognostic SNP role, attention was paid not only to the genes encoding the main receptor ACE2 and the co-receptor TMPRSS2 through which SARS-CoV-2 enters the target cell, but also to the APOE gene encoding the lipoprotein Apo E, which is a multifunctional protein involved in lipid metabolism and a structural component of cell membranes. It is known that there are three isoforms, namely APO E2, APO E3 and APO E4, respectively, with SNPs of this gene at positions 112 and 158 [25].

Previous studies have demonstrated the association between APOE E4 and infectious diseases of viral etiology, in particular, hepatitis C virus, human immunodeficiency virus infection, and herpes simplex virus infection [26]. Specifically, in hepatitis C, the APOE E4 genotype is associated with a low risk of chronicity and slower fibrosis, and in human immunodeficiency virus infection, on the contrary, with accelerated progression of immunodeficiency [26]. When infected with herpes simplex virus APOE E4, the genotype is associated with increased viral persistence in cells of the central nervous system, which may increase the risk of developing Alzheimer's disease [26]. In the new coronavirus disease, the influence of the APOE E4 genotype on the clinical course of COVID-19 has also been documented, which has a certain pathogenetic explanation.

According to [27], E4 carriers have elevated levels of circulating and tissue-specific cholesterol, as well as elevated levels of low-density lipoprotein directly in pneumocytes and pulmonary macrophages, which is the cause of increased accumulation of ACE2 and TMPRSS2 in cholesterol-rich domains. Researchers [27] believe that cholesterol enrichment of target cell membranes may be a critical factor in determining the risk of SARS-CoV-2 infection. The meta-analysis has confirmed the above pattern and proved that APOE E4E4 and E3E3 genotypes were associated with a 23.6 % increase in the risk of SARS-CoV-2 infection. At the same time, the APOE E4E4 genotype increased the risk of human infection with COVID-19 by 20.9 % and 22.8 % compared to the APOE E3E4 and APOE E3E3 + E3E4 genotypes, respectively [10].

Clinical and prognostic significance of SNP in human genes encoding immune response. Since the human leukocyte antigen (HLA) system is directly involved in the formation of an effective antiviral cellular immune response, HLA genes immediately caught the attention as a potential marker of susceptibility to COVID-19 and the disease severity [28]. According to the results of a study [29], it has been proved that in the presence of HLA-B*46:01, the number of presented binding peptides for SARS-CoV-2 was the lowest. This explains the association with a higher risk of SARS-CoV-2 infection, while HLA-B*15:03 had the highest ability to present highly conserved SARS-CoV-2 peptides, which are also present in other human coronaviruses allowing for cross-talk in T-cell responses. Other researchers [30] have shown that HLA-C*04:01 was clearly linked to the risk of severe COVID-19 and an almost twofold increased risk of acute respiratory failure requiring mechanical ventilation. In addition, SNP rs660895 (GA genotype) of HLA-DRB1 and HLA-DRB5 has been shown to correlate with increased serum interleukin-6 (IL-6) levels in SARS-CoV-2 infected individuals being associated with a more severe course of COVID-19 [31].

A series of studies have shown that dysregulation of innate immunity, which determines early control of SARS-CoV-2 infection, leads to hyperinflammation and, consequently, a more severe course of the disease and the risk of death [32,33]. Therefore, it was immediately suggested that SNP of innate immune system genes should be assessed as risk factors for COVID-19 outcome. For example, a study [34] has shown that SNP in the IL-18 gene at the rs1834481 locus was an independent risk factor for pneumonia. SNP in the TLR2 gene at the rs5743708 locus and the TLR4 gene at the rs4986791 locus increased the risk of severe SARS-CoV-2-associated pneumonia by 3.6 and 2.5 times, respectively [34]. After obtaining the above results, the authors confirmed the assumption of a significant influence of the host's genetic background on the clinical phenotype of COVID-19 and suggested the use of established predictors in clinical practice [34].

It is known that the interferon (IFN) system plays a major role in antiviral defense. For example, interferon-induced transmembrane protein 3 (IFITM3) limits the spread of many viruses in the human body, including influenza A virus, which is capable of pandemic spread [35]. The antiviral effect of IFITM3 is associated with its dimerization in endolysosomal membranes preventing the virus from entering the cell cytoplasm [36]. SNP in the IFITM3 gene at the rs12252 locus has a clear clinical and pathogenetic significance as it leads to the formation of a truncated protein in the N-terminal region which consequently causes its inability to provide antiviral protection. A meta-analysis has demonstrated a relationship between SNP in the IFITM3 gene at the rs12252 locus and both susceptibility to influenza and its severity, namely, the association between the CC genotype and a higher risk of severe influenza [37]. A similar pattern regarding the SNP role in the IFITM3 gene has been found in another meta-analysis in relation to COVID-19 [10]. The C-allele of the IFITM3 gene at the rs12252 locus and the CC genotype were found to cause 19.0 % and 58.7 % higher chances of SARS-CoV-2 infection compared to the T-allele and TT genotype, respectively. In COVID-19, the association between SNP in the IFITM3 gene at the rs12252 locus and an increased risk of SARS-CoV-2 infection is also explained by the reduced antiviral activity of IFITM3 in carriers of this mutation [10]. In addition, SNP rs10735079 in the IFN-induced antiviral oligoadenylate synthase 1 and 3 genes is associated with an increased

risk of hospitalization in patients with COVID-19 [38]. SNP role in IFN genes has been demonstrated in other studies. In particular, rs28368148 (CG genotype) of the IFN-α gene has been shown to have a strong association with severe COVID-19 [39].

Based on many studies, cytokine gene polymorphism has demonstrated a clear impact on the risk of developing the so-called "cytokine storm" and, consequently, on the severity of COVID-19 [19,32,40,41]. IL-6 is known to be one of the leading cytokines, the degree of increase in which is clearly correlated with the "cytokine storm" development. SNP in the IL-6R gene (rs4537545, TC genotype) was associated with the highest serum IL-6 levels, which was correlated with the severity of COVID-19 [32]. Given this genetic risk factor for the development of severe and critical course of COVID-19, researchers have drawn attention to the certain expediency of taking this genetic factor into account when deciding on treatment correction with the use of drugs for which IL-6 is the main target [32].

To determine the role of SNP in the tumor necrosis factor-α (TNF-α) gene G-308 A, 900 patients with COVID-19 and 184 control subjects were examined. It has been proved that 80.0 % of patients with the AA genotype had a severe course of the disease compared to 41.7 % of patients with the GA genotype, while the authors did not observe severe COVID-19 in any case with the GG genotype of the TNF-α gene. According to researchers, in patients with prognostically unfavorable AA genotype of the TNF-α gene, the use of anti-TNF-α monoclonal antibodies could be a promising direction in individualizing treatment [40].

In addition, an analysis of the Italian population has shown that SNP in the chemokine receptor gene CCR5, namely at the loci rs9845542, rs12639314 and rs35951367 (GT genotypes), were associated with reduced CCR5 expression in lung tissue and, accordingly, were related to an increased risk of severe COVID-19 [41].

The prognostic role of elevated serum levels of C-reactive protein (CRP) in patients with COVID-19, which can reach extremely high levels, was proven at the beginning of the pandemic [42]. Proinflammatory cytokines, in particular IL-6 and TNF-α, which are produced in excessive amounts during the "cytokine storm", significantly stimulate CRP production by hepatocytes [43]. Therefore, according to the results of a series of studies [42,44], CRP has been proposed to be used as a biomarker of COVID-19 severity and risk of death. Molecular genetic studies have demonstrated a relationship between serum CRP elevation and mortality in patients with COVID-19 and SNP in the CRP gene [45].

Thus, based on the results of genotyping the CRP gene SNP at the rs1205 and rs1800947 loci in 2023 patients who died as a result of COVID-19 and 2307 patients who recovered, a significant difference in the frequency of minor alleles was found: T-allele of CRP at the rs1205 locus and G-allele at the rs1800947 locus. The risk of death from COVID-19 was clearly associated with the GG genotype of the CRP gene at the rs1800947 locus. Furthermore, it should be noted that in patients with COVID-19, the CC genotype of the CRP gene at the rs1205 locus and the GG genotype of the CRP gene at the rs1800947 locus were associated with significantly higher serum CRP levels [45]. Particularly noteworthy are the results of a meta-analysis [46] showing that association between SNP in the CRP gene at the rs67579710 locus and the thrombospondin-3 gene influences not only the severity of immune inflammation but also the risk of developing thrombotic complications.

In a developing clinically significant form of COVID-19, some patients show signs of liver damage. At the same time, not only liver damage due to the hepatotoxic effects of certain drugs used in the treatment of COVID-19, but also the influence of genetic factors on the development of hepatic consequences of SARS-CoV-2 infection is currently being considered [47,48,49]. Researchers [47] have reported that, regardless of the treatment prescribed, patients with the membrane-bound O-acyltransferase domain of the corresponding gene at the rs641738 locus had a significant increase in total bilirubin levels, biochemical signs of cytolytic syndrome with increased alanine aminotransferase activity and intrahepatic cholestasis syndrome with increased alkaline phosphatase activity, combined with a decrease in serum albumin levels at hospitalization, indicating a genetic predisposition [47].

Other researchers have also revealed the influence of certain genetic factors on the liver damage degree. For example, SNP at the rs11385942 G>GA locus in the chromosome 3 gene cluster and SNP at the rs657152 C>A locus of the ABO system were clearly associated with the severity of liver damage, that was diagnosed during hospitalization of patients with SARS-CoV-2 infection [48,49].

Prognostic significance of host gene SNPs in the development of fatal thrombotic complications in COVID-19**.** It is known that high levels of D-dimer and CRP are biomarkers for predicting the risk of thrombotic complications, the development of which leads to increased mortality in patients with severe COVID-19 [50]. It has been suggested that complex genetic chains may underlie the predisposition to thrombotic events in patients with COVID-19 [51,52].

Authors of study [51] retrospectively assessed a number of gene SNP distribution that might be associated with thrombotic risk in patients with COVID-19 who developed pulmonary embolism (PE) or did not develop PE. The main findings of this study demonstrated a significantly higher percentage of homozygous mutant genotypes of ACE (genotype DD) and APOE (genotype CC) in patients with PE compared to patients without this thrombotic complication. In addition, in patients with PE, the level of D-dimer elevation was significantly higher in carriers of the DD and ID genotypes of the ACE gene and in carriers of the CC and TC genotypes of the APOE gene [51]. The authors of the study have formulated a certain pathogenetic explanation for the ACE gene SNP role in the formation of higher levels of D-dimer and, accordingly, the PE risk. It has been suggested that an imbalance in ACE/ACE2 receptor levels, which is inherent in the DD and ID genotypes of the ACE gene, may induce endothelial cell apoptosis, resulting in prolonged hypercoagulation and, hence, a greater level of D-dimer elevation and risk of developing PE in patients with COVID-19 [51].

Since it was previously known about the racial difference in the ACE gene SNPs, namely the prevalence of the D-allele in European populations (82–87 %), and the I-allele in East Asian populations (33–51 %) [53], the estimated prognostic significance of the ACE gene SNP allowed to explain the higher incidence of fatal thrombotic complications in a number of European countries (Spain, Italy, France) [51].

The role of host gene SNPs in developing long COVID. Since many studies have shown the role of human genetic polymorphism as a critical factor in shaping the severity of COVID-19 clinical symptoms and the risk of adverse outcomes, at a certain stage of studying the new coronavirus disease, the question arose about clarifying the role of host gene SNPs in developing long-term symptoms of long COVID [54]. Currently, long COVID is defined as the presence of persistent long-term symptoms after SARS-CoV-2 infection for at least four weeks after the onset of symptoms in individuals with laboratory confirmation of COVID-19 [54]. On the one hand, the long-term clinical symptoms of COVID-19 can be explained by old age and comorbidities [55], but on the other hand, severe consequences of this disease and long COVID have been reported in young people without comorbidities [56]. The above indicates the presence of genetic risk factors for long COVID which currently needs to be studied. In the current literature, there are already studies focused on clarifying the role of genetic factors in the development of long COVID [54].

Thus, researchers [54] have identified possible relationships between SNPs in 37 candidate genetic variants and the development of clinical signs of long COVID. The study has shown that both SNP of genes encoding receptors responsible for SARS-CoV-2 entry into target cells and SNP of genes encoding immune responses were associated with the risk of long COVID. SNP of the ACE2 gene at the rs2285666 locus, namely the CC genotype, has been shown to be associated with a significant reduction in the risk of developing long COVID, in contrast to the CT and TT genotypes, which were associated with a high risk of developing long-term manifestations of the disease [54].

SNP of cytokine genes and their receptors also play a role in the development of long COVID. In particular, with SNP of the IL-10 gene at the rs1800896 locus, namely the TC and CC genotypes, the risk of developing long COVID is statistically significantly higher than that with the TT genotype [54]. In addition, a SNP of the IL-10 receptor at the rs8178562 locus, namely the GG genotype, has a high association with the risk of developing long COVID compared to the AA and GA genotypes [54].

Conclusions

1. SNP of host genes encoding receptors responsible for the entry of SARS-CoV-2 into target cells and SNP of genes encoding immune responses have some prognostic value in assessing the risk of severe disease and adverse outcomes of COVID-19.

2. The accumulation of data on genetic risk factors for adverse outcomes of the new coronavirus disease 2019 will allow us to enhance the understanding of this infection pathogenesis, improve patient stratification and individualize therapeutic interventions.

Prospects for further research. In our opinion, further research on the role of genetic factors in assessing the characteristics of the course and consequences of the new coronavirus disease 2019 will allow us to establish informative markers for patient stratification and create certain directions in the development of individualized pharmacological treatment.

Conflicts of interest: authors have no conflict of interest to declare.
Конфлікт інтересів: відсутній.

Надійшла до редакції / Received: 28.06.2024
Після доопрацювання / Revised: 06.08.2024
Схвалено до друку / Accepted: 28.08.2024

Information about the authors:
Riabokon Yu. Yu., MD, PhD, DSc, Professor of the Department of Children Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0002-2273-8511
Huseynov E. M., MD, PhD, DSc, Associate Professor of the Department of Infectious Diseases, Azerbaijan Medical University, Baku.
ORCID ID: 0000-0003-4427-6722
Kalashnyk K. V., MD, PhD, Associate Professor of the Department of Infectious Diseases, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0002-4532-8953

Відомості про авторів:
Рябоконь Ю. Ю., д-р мед. наук, професор каф. дитячих інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.
Гусейнов Е. М., д-р мед. наук, доцент каф. інфекційних хвороб, Азербайджанський медичний університет, м. Баку.
Калашник К. В., PhD, доцент каф. інфекційних хвороб, Запорізький державний медико-фармацевтичний університет, Україна.

References

1. Mukherjee S, Huda S, Sinha Babu SP. Toll-like receptor polymorphism in host immune response to infectious diseases: A review. Scand J Immunol. 2019;90(1):e12771. doi: 10.1111/sji.12771
2. Keshavarz M, Namdari H, Farahmand M, Mehrbod P, Mokhtari-Azad T, Rezaei F. Association of polymorphisms in inflammatory cytokines encoding genes with severe cases of influenza A/H1N1 and B in an Iranian population. Virol J. 2019;16(1):79. doi: 10.1186/s12985-019-1187-8
3. Naranjo-Galvis CA, de-la-Torre A, Mantilla-Muriel LE, Beltrán-Angarita L, Elcoroaristizabal-Martín X, McLeod R, et al. Genetic Polymorphisms in Cytokine Genes in Colombian Patients with Ocular Toxoplasmosis. Infect Immun. 2018;86(4):e00597-17. doi: 10.1128/IAI.00597-17
4. Zhang M, Xu J, Bao X, Niu W, Wang L, Du L, et al. Association between Genetic Polymorphisms in Interleukin Genes and Recurrent Pregnancy Loss – A Systematic Review and Meta-Analysis. PLoS One. 2017;12(1):e0169891. doi: 10.1371/journal.pone.0169891
5. Chen Y, Hu Y, Song Z. The association between interleukin-6 gene -174G/C single nucleotide polymorphism and sepsis: an updated meta-analysis with trial sequential analysis. BMC Med Genet. 2019;20(1):35. doi: 10.1186/s12881-019-0766-2
6. Wang J, Fan N, Deng Y, Zhu J, Mei J, Chen Y, Yang H. Association between genetic polymorphisms of interleukins and cerebral infarction risk: a meta-analysis. Biosci Rep. 2016;36(6):e00404. doi: 10.1042/BSR20160226
7. Hishida A, Okugawa Y, Morimoto Y, Shirai Y, Okamoto K, Momokita S, et al. Genetic influence of cytokine polymorphisms on the clinical outcome of Japanese gastrointestinal cancer patients in palliative care. Oncol Lett. 2019;17(1):623-9. doi: 10.3892/ol.2018.9614
8. Alipoor SD, Mortaz E, Jamaati H, Tabarsi P, Bayram H, Varahram M, et al. COVID-19: Molecular and Cellular Response. Front Cell Infect Microbiol. 2021;11:563085. doi: 10.3389/fcimb.2021.563085
9. Rithanya M, Brundha MP. Molecular Immune Pathogenesis and Diagnosis of COVID-19 – A Review. Int J Cur Res Rev. 2020;12(21):69-73. doi: 10.31782/ijcrr.2020.sp37
10. Gupta K, Kaur G, Pathak T, Banerjee I. Systematic review and meta-analysis of human genetic variants contributing to COVID-19 susceptibility and severity. Gene. 2022;844:146790. doi: 10.1016/j.gene.2022.146790
11. David S, Dorado G, Duarte EL, David-Bosne S, Trigueiro-Louro J, Rebelo-de-Andrade H. COVID-19: impact on Public Health and hypothesis-driven investigations on genetic susceptibility and severity. Immunogenetics. 2022;74(4):381-407. doi: 10.1007/s00251-022-01261-w
12. Adli A, Rahimi M, Khodaie R, Hashemzaei N, Hosseini SM. Role of genetic variants and host polymorphisms on COVID-19: From viral entrance mechanisms to immunological reactions. J Med Virol. 2022;94(5):1846-65. doi: 10.1002/jmv.27615

13. Scaramuzzo G, Nucera F, Asmundo A, Messina R, Mari M, Montanaro F, et al. Cellular and molecular features of COVID-19 associated ARDS: therapeutic relevance. J Inflamm (Lond). 2023;20(1):11. doi: 10.1186/s12950-023-00333-2
14. Singh H, Choudhari R, Nema V, Khan AA. ACE2 and TMPRSS2 polymorphisms in various diseases with special reference to its impact on COVID-19 disease. Microb Pathog. 2021;150:104621. doi: 10.1016/j.micpath.2020.104621
15. Gard PR. Implications of the angiotensin converting enzyme gene insertion/deletion polymorphism in health and disease: a snapshot review. Int J Mol Epidemiol Genet. 2010;1(2):145-57.
16. Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. Clin Chim Acta. 2020;505:192-3. doi: 10.1016/j.cca.2020.03.031
17. Kenyon C. ACE-1 I/D Polymorphism Associated with COVID-19 Incidence and Mortality: An Ecological Study. Preprints. 2020;19(April),1-37. 10.20944/preprints202004.0262.v1
18. Yamamoto N, Ariumi Y, Nishida N, Yamamoto R, Bauer G, Gojobori T, et al. SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. Gene. 2020;758:144944. doi: 10.1016/j.gene.2020.144944
19. Wang J, Xu X, Zhou X, Chen P, Liang H, Li X, et al. Molecular simulation of SARS-CoV-2 spike protein binding to pangolin ACE2 or human ACE2 natural variants reveals altered susceptibility to infection. J Gen Virol. 2020;101(9):921-4. doi: 10.1099/jgv.0.001452
20. Srivastava A, Bandopadhyay A, Das D, Pandey RK, Singh V, Khanam N, et al. Genetic Association of *ACE2* rs2285666 Polymorphism With COVID-19 Spatial Distribution in India. Front Genet. 2020;11:564741. doi: 10.3389/fgene.2020.564741
21. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-92. doi: 10.1038/s41579-018-0118-9
22. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280.e8. doi: 10.1016/j.cell.2020.02.052
23. Asselta R, Paraboschi EM, Mantovani A, Duga S. *ACE2* and TMPRSS2 variants and expression as candidates to sex and country differences in COVID-19 severity in Italy. Aging (Albany NY). 2020;12(11):10087-98. doi: 10.18632/aging.103415
24. Stopsack KH, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. TMPRSS2 and COVID-19: Serendipity or Opportunity for Intervention? Cancer Discov. 2020;10(6):779-82. doi: 10.1158/2159-8290.CD-20-0451
25. Tudorache IF, Trusca VG, Gafencu AV. Apolipoprotein E – A Multifunctional Protein with Implications in Various Pathologies as a Result of Its Structural Features. Comput Struct Biotechnol J. 2017;15:359-65. doi: 10.1016/j.csbj.2017.05.003
26. Kuhlmann I, Minihane AM, Huebbe P, Nebel A, Rimbach G. Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: a literature review. Lipids Health Dis. 2010;9:8. doi: 10.1186/1476-511X-9-8
27. Gkouskou K, Vasilogiannakopoulou T, Andreakos E, Davanos N, Gazouli M, Sanoudou D, et al. COVID-19 enters the expanding network of apolipoprotein E4-related pathologies. Redox Biol. 2021;41:101938. doi: 10.1016/j.redox.2021.101938
28. Zunec R. A review of HLA and COVID-19 association studies. Molecular and experimental biology in medicine. 2020;3(2):25-30. doi: 10.33602/mebm.3.2.3
29. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, Thompson RF. Human Leukocyte Antigen Susceptibility Map for Severe Acute Respiratory Syndrome Coronavirus 2. J Virol. 2020;94(13):e00510-20. doi: 10.1128/JVI.00510-20
30. Weiner J, Suwalski P, Holtgrewe M, Rakitko A, Thibeault C, Müller M, et al. Increased risk of severe clinical course of COVID-19 in carriers of HLA-C*04:01. EClinicalMedicine. 2021;40:101099. doi: 10.1016/j.eclinm.2021.101099
31. Ahluwalia TS, Prins BP, Abdollahi M, Armstrong NJ, Aslibekyan S, Bain L, et al. Genome-wide association study of circulating interleukin 6 levels identifies novel loci. Hum Mol Genet. 2021;30(5):393-409. doi: 10.1093/hmg/ddab023
32. Diamond MS, Kanneganti TD. Innate immunity: the first line of defense against SARS-CoV-2. Nat Immunol. 2022;23(2):165-76. doi: 10.1038/s41590-021-01091-0
33. Paludan SR, Mogensen TH. Innate immunological pathways in COVID-19 pathogenesis. Sci Immunol. 2022;7(67):eabm5505. doi: 10.1126/sciimmunol.abm5505
34. Bakaros E, Voulgaridi I, Paliatsa V, Gatselis N, Germanidis G, Asvestopoulou E, et al. Innate Immune Gene Polymorphisms and COVID-19 Prognosis. Viruses. 2023;15(9):1784. doi: 10.3390/v15091784
35. Spence JS, He R, Hoffmann HH, Das T, Thinon E, Rice CM, et al. IFITM3 directly engages and shuttles incoming virus particles to lysosomes. Nat Chem Biol. 2019;15(3):259-68. doi: 10.1038/s41589-018-0213-2
36. Bailey CC, Zhong G, Huang IC, Farzan M. IFITM-Family Proteins: The Cell's First Line of Antiviral Defense. Annu Rev Virol. 2014;1:261-83. doi: 10.1146/annurev-virology-031413-085537
37. Prabhu SS, Chakraborty TT, Kumar N, Banerjee I. Association between IFITM3 rs12252 polymorphism and influenza susceptibility and severity: A meta-analysis. Gene. 2018;674:70-9. doi: 10.1016/j.gene.2018.06.070
38. Banday AR, Stanifer ML, Florez-Vargas O, Onabajo OO, Papenberg BW, Zahoor MA, et al. Genetic regulation of OAS1 nonsense-mediated decay underlies association with COVID-19 hospitalization in patients of European and African ancestries. Nat Genet. 2022;54(8):1103-16. doi: 10.1038/s41588-022-01113-z
39. Kousathanas A, Pairo-Castineira E, Rawlik K, Stuckey A, Odhams CA, Walker S, et al. Whole-genome sequencing reveals host factors underlying critical COVID-19. Nature. 2022;607(7917):97-103. doi: 10.1038/s41586-022-04576-6
40. Saleh A, Sultan A, Elashry MA, Farag A, Mortada MI, Ghannam MA, et al. Association of TNF-α G-308 a Promoter Polymorphism with the Course and Outcome of COVID-19 Patients. Immunol Invest. 2022;51(3):546-57. doi: 10.1080/08820139.2020.1851709
41. Cantalupo S, Lasorsa VA, Russo R, Andolfo I, D'Alterio G, Rosato BE, et al. Regulatory Noncoding and Predicted Pathogenic Coding Variants of *CCR5* Predispose to Severe COVID-19. Int J Mol Sci. 2021;22(10):5372. doi: 10.3390/ijms22105372
42. Stringer D, Braude P, Myint PK, Evans L, Collins JT, Verduri A, et al. The role of C-reactive protein as a prognostic marker in COVID-19. Int J Epidemiol. 2021;50(2):420-9. doi: 10.1093/ije/dyab012
43. Ponti G, Maccaferri M, Ruini C, Tomasi A, Ozben T. Biomarkers associated with COVID-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-99. doi: 10.1080/10408363.2020.1770685
44. Tahery N, Khodadost M, Jahani Sherafat S, Rezaei Tavirani M, Ahmadi N, Montazer F, et al. C-reactive protein as a possible marker for severity and mortality of COVID-19 infection. Gastroenterol Hepatol Bed Bench. 2021 Fall;14(Suppl1):S118-S122.
45. Sadeghi Mofrad S, Boozarjomehri Amnieh S, Pakzad MR, Zardadi M, Ghazanfari Jajin M, Anvari E, et al. The death rate of COVID-19 infection in different SARS-CoV-2 variants was related to C-reactive protein gene polymorphisms. Sci Rep. 2024;14(1):703. doi: 10.1038/s41598-024-51422-y
46. COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature. 2021;600(7889):472-7. doi: 10.1038/s41586-021-03767-x
47. Machill A, Bals R, Lammert F, Krawczyk M. Genetic insight into COVID-19 related liver injury: A note on MBOAT7. Liver Int. 2021;41(5):1157-9. doi: 10.1111/liv.14732
48. Bianco C, Baselli G, Malvestiti F, Santoro L, Pelusi S, Manunta M, et al. Genetic insight into COVID-19-related liver injury. Liver Int. 2021;41(1):227-9. doi: 10.1111/liv.14708
49. Valenti L, Griffini S, Lamorte G, Grovetti E, Uceda Renteria SC, Malvestiti F, et al. Chromosome 3 cluster rs11385942 variant links complement activation with severe COVID-19. J Autoimmun. 2021;117:102595. doi: 10.1016/j.jaut.2021.102595
50. Gorog DA, Storey RF, Gurbel PA, Tantry US, Berger JS, Chan MY, et al. Current and novel biomarkers of thrombotic risk in COVID-19: a Consensus Statement from the International COVID-19 Thrombosis Biomarkers Colloquium. Nat Rev Cardiol. 2022;19(7):475-95. doi: 10.1038/s41569-021-00665-7
51. Fiorentino G, Benincasa G, Coppola A, Franzese M, Annunziata A, Affinito O, et al. Targeted genetic analysis unveils novel associations between ACE I/D and APO T158C polymorphisms with D-dimer levels in severe COVID-19 patients with pulmonary embolism. J Thromb Thrombolysis. 2023;55(1):51-9. doi: 10.1007/s11239-022-02728-z
52. Jukic I, Heffernan A, Schelling AF, Kokic Males V, Savicevic NJ, Kovacic V. Association between COVID-19 Infection or Vaccination Outcomes and Methylenetetrahydrofolate Reductase Gene Polymorphism: A Systematic Review of the Literature. J Pers Med. 2023;13(12):1687. doi: 10.3390/jpm13121687
53. Saab YB, Gard PR, Overall AD. The geographic distribution of the ACE II genotype: a novel finding. Genet Res. 2007;89(4):259-67. doi: 10.1017/S0016672307009019
54. Udomsinprasert W, Nontawong N, Saengsiwaritt W, Panthan B, Jiaranai P, Thongchompoo N, et al. Host genetic polymorphisms involved in long-term symptoms of COVID-19. Emerg Microbes Infect. 2023;12(2):2239952. doi: 10.1080/22221751.2023.2239952
55. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3
56. Abou-Ghaida J, Foster A, Klein S, Bassie M, Gu K, Hille C, et al. The World-Wide Adaptations of Diabetic Management in the Face of COVID-19 and Socioeconomic Disparities: A Scoping Review. Cureus. 2022;14(11):e31911. doi: 10.7759/cureus.31911