GENETIC BASIS FOR SEVERE COVID-19

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Abstract. COVID-19 is a disease first reported in 2019 that claimed the lives of more than 6.5 million people worldwide, paralyzed transport links and locked the borders of many states for a long time. In 2023, 3 years have passed since, yet not all countries have fully recovered and lifted the restrictions, which, of course, highlights that COVID-19 has had a huge impact on all aspects of modern life. The pandemic has given a strong impetus to the development of science and the study of COVID-19 and infectious diseases in general around the world, many articles on COVID-19 have been published in the past 3 years. Particularly interesting was the fact that while some people were asymptomatic, had mild COVID-19, other patients required mechanical ventilation and even medically induced coma. In this regard, the study of the genetic factors contributing to the severe course of the disease, comorbidities and the individual response to drugs has become especially relevant. In our work, we consider the main genes and entire loci of chromosomes involved in the pathogenesis of COVID-19. Genes such as IFNAR2, TMPRSS2, ACE2, TYK2, DPP9, HLA, OAS3, ABO, 3p21.31 locus and 12q24.13 locus have been considered; in addition, the association of severe COVID-19 with diseases such as type 2 diabetes, cardiovascular disease and obesity was discussed.

Keywords: COVID-19, human, genes.

List of Abbreviations

ADRP – ADP-ribose phosphatase domain
BBS – Bardet-Biedl syndrome
COPD – Chronic obstructive pulmonary disease
COVID-19 – Coronavirus disease 2019
CVD – Cardiovascular disease
EMT – Epithelial-mesenchymal transition
GWAS – Genome-wide association study
MERS – Middle East respiratory syndrome
NendoU – Endoribonuclease
NSPs – Non-structural proteins
ORFs – Open reading frames
PTB – Polypyrimidine tract-binding protein
RBD – Receptor-binding domain
RBM – Receptor binding motif
RdRp – RNA-dependent RNA polymerase
RNA – Ribonucleic acid
RNase L – Ribonuclease L
RTC – Replication transcription complex
SARS – Severe acute respiratory syndrome
SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2
sub-gRNAs – Sub-genomic RNAs
UTRs – Untranslated regions
WES – Whole exome sequencing

Introduction

A new strain of coronavirus – SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was first detected in Wuhan, China at the end of 2019 and caused an outbreak of a new highly contagious disease, COVID-19, which quickly spread around the world. It is well documented that the course of disease varies from asymptomatic to severe. According to the World Health Organization (WHO), as of March 2023, there were more than 760 million confirmed cases of COVID-19, including more than 6 million deaths. The SARS-CoV-2 virus belongs to the family *Coronaviridae*, genus *Betacoronavirus*, subgenus *Sarbecovirus* (Nikonova *et al.*, 2021). Coronaviruses are a diverse group of viruses that can infect a variety of animals as well as humans. We have previously witnessed outbreaks of other coronavirus diseases in 2002 and 2012 such as SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), however COVID-19 far surpassed them in terms of the number of infected people and the scale of the pandemic (Hu *et al.*, 2021).

In this review, we described the main characteristics of the SARS-CoV-2 virus genome and discussed the relationship between certain genes and the severe course of COVID-19.

1. General characteristics of the SARS-CoV-2 virus genome

The genetic material of the SARS-CoV-2 virus is a single-stranded, positive-sense RNA of a relatively large size of 29,903 bp. The viral cell has a shape of a sphere with spike-like protrusions on the lipid membrane, which are actually glycoproteins that facilitate entry into host cells. SARS-CoV-2 shares 79% genome sequence identity with SARS-CoV and 50% with MERS-CoV. Its genome is similar to other betacoronaviruses. It is also reported that the genome sequence of SARS-CoV-2 is 96.1% similar to bat coronaviruses RaTG13 and 93.3% similar to RmYN02 (H. Zhou *et al.*, 2020; P. Zhou *et al.*, 2020).

The RNA molecule includes 5' and 3' untranslated regions, and there are also open reading frames (ORFs) the longest of which is ORF1a, that accounts for about two-thirds of the genome. This region encodes 16 non-structural proteins (NSPs). Inside the host cell, pp1a and pp1a/b polyproteins are synthesized from such open reading frames as ORF1a and ORF1ab, which are cleaved by the main protease (Mpro/3CLpro) and papain-like protease to form 16 different NSPs. These NSPs then form a replication transcription complex (RTC) for the synthesis of genomic and sub-genomic RNAs (sub-gRNAs) that encode structural and accessory proteins. Researchers conclude that Mpro could be a target for drug development against SARS-CoV-2 (Kadam *et al.*, 2021). ORF1a and ORF1b are followed by shorter subgenomic RNAs encoding four structural proteins such as spike protein S (spike), envelope protein E (envelope), membrane protein M (membrane) and nucleocapsid protein N (nucleocapsid), as well as several other accessory proteins (Garafutdinov *et al.*, 2020; Kadam *et al.*, 2021). The genome of the SARS-CoV-2 virus includes a total of 6 to 11 ORF sequences. These genes carry important information about the structure of the virus, which has been preserved for many generations (Khan *et al.*, 2022).

In many other coronaviruses, host factors can also interact with the cis-acting 5' and 3' untranslated regions (UTRs) of the viral RNA and take part in viral RNA synthesis. These factors include heterogeneous nuclear ribonucleoproteins A1 and Q, polypyrimidine tract-binding protein (PTB), and poly(A)-binding protein (Chen & Olsthoorn, 2010; Nakagawa *et al.*, 2016).

1.1. Functions of nonstructural proteins

Let us consider the types of some non-structural proteins and their functions in more detail. The first of these is NSP1, which can block the synthesis of antiviral protein by interacting with the small subunit of the human ribosome. NSP1 accomplishes this by shutting down host protein synthesis in infected cells. Schubert K. et al. showed how translation is suppressed in the presence of NSP1 in the in vitro translation system and in human cells (Schubert *et al.*, 2020). It is noteworthy that the amino acid sequence of the NSP1 protein of SARS-CoV and SARS-CoV-2 is 84% identical, which indicates similar functional of NSP1 in both viruses. The next protein, NSP2, interacts with signals that are present in the host cell cycle. For example, in SARS-CoV, NSP2 specifically interacts with human proteins involved in the functioning of mitochondria and cell proliferation. It has been suggested that NSP2 may be involved in disruption of host intracellular signaling during SARS-CoV infections (Cornillez-Ty *et al.*, 2009). NSP3 is a large polyfunctional protein that encodes the SARS-CoV-2 genome. This protein has several domains, one of which is the ADP-ribose phosphatase (ADRP) domain associated with host immune signaling; researchers suggest it plays an important role in causing a cytokine storm in host tissue, which is the main cause of severe COVID-19 (Kadam *et al.*, 2021).

There is also discussion regarding the possible role of the ADRP domain in enhancing ACE2 expression, thus accelerating the multiplication of SARS-CoV-2 inside the host cells (Kadam *et al.*, 2021). In addition, NSP3 has an-

other important function: it encodes papain-like protease (PLpro) (Klemm *et al.*, 2020). PLpro cleaves NSP1, NSP2 and NSP3 from the long polypeptide chain. NSP3 is also involved in forming double-membrane vesicles by interacting with NSP4. NSP5 (Mpro/3CLpro) also has proteolytic activity. The non-structural proteins NSP3 and NSP5 perform the first protein cleavage within the host cell. Interestingly, Mpro SARS-CoV-2 differs from Mpro SARS-CoV, as in Mpro SARS-CoV-2, threonine is replaced by alanine at position 285, which leads to an increase in its catalytic activity (Zhang *et al.*, 2020). The non-structural protein NSP12, a catalytic subunit of RNA-dependent RNA polymerase (RdRp), acts in order to enhance the activity of the enzyme, the NSP7-NSP8 heterodimer binds and an additional copy of NSP8 is produced. The RdRp complex is involved in SARS-CoV-2 genome replication and gene transcription. The structure is similar to SARS-CoV RdRp. The researchers note that the RdRp complex is a target for nucleoside analog inhibitors, such as remdesivir, which is an antiviral drug (Hillen *et al.*, 2020). NSP15 is endoribonuclease (NendoU) that protects the virus from the host's immune response. Due to its concave surface shape, it can interact with other proteins and RNA (Kadam *et al.*, 2021). NSP14 has two distinct functions: exoribonuclease activity and N7-guanine methyltransferase activity. NSP10 is an activator of NSP14. Next is NSP13, which is the helicase of the virus. And NSP16 is a methyltransferase, one of the conserved proteins among coronaviruses, which forms a complex with NSP10. The NSP9 is among the main proteins for virus amplification. It is believed to be involved in RNA replication (Garafutdinov *et al.*, 2020; Kadam *et al.*, 2021).

Accessory proteins also exist, which are possibly involved in counteracting the host's immune response (Kadam *et al.*, 2021).

1.2. Functions of structural proteins

The spike protein S has attracted much attention because the SARS-CoV-2 virus relies on it when entering the host cell, interacting with host receptors (the ACE2 receptor). The S protein itself consists of two subunits, S1 and S2, and between them there is a furin cleavage site (RRAR), which distinguishes SARS-CoV-2 from SARS-CoV and other betacoronaviruses. Another unique feature of SARS-CoV-2 is the addition of a proline residue at the beginning of the furin cleavage site (Hu *et al.*, 2021). There is evidence that the region that binds to ACE2 is highly conserved among coronaviruses (Vandelli *et al.*, 2020). The S1 subunit is responsible for binding to the ACE2 receptor, and the subsequent fusion of the viral envelope with the cell membrane occurs with the help of the S2 subunit. The S1 subunit contains a key functional component, the receptor-binding domain (RBD), which is responsible for ACE2 recognition and virus entry, it is argued that any mutation in RBD can affect its binding to the receptor (Garafutdinov *et al.*, 2020). The receptor-binding domain of SARS-CoV-2 and SARS-CoV are only 73% similar in amino acid sequence (Hu *et al.*, 2021). This domain contains a receptor binding motif (RBM) that mediates contacts with the ACE2 receptor. There are two points on the surface of ACE2 that SARS-CoV-2 uses for attachment (Nikonova *et al.*, 2021). According to biochemical data, the structural features of the SARS-CoV-2 RBD increased its binding affinity for ACE2 compared to SARS-CoV (Letko *et al.*, 2020; Shang *et al.*, 2020). It should be noted that SARS-CoV-2 entry into the cell also depends on the transmembrane serine protease TMPRSS2, which is involved in the priming of viral proteins and is tissue-specifically expressed in alveolar cells. Researchers consider TMPRSS2 to be a potential target for COVID-19 therapy (Zarubin *et al.*, 2020).

The next structural protein is the envelope protein E, represented by a small polypeptide. Protein E is involved in the formation of ion channels and in the formation of viroporins, which are involved in the assembly and release of viral particles (Garafutdinov *et al.*, 2020; Kadam *et al.*, 2021; Nikonova *et al.*, 2021). The M membrane protein plays an important role in virus assembly and its internal homeostasis. It is the most abundant protein on the surface of the virus. The nucleocapsid protein N forms a ribonucleoprotein complex with viral RNA and is

involved in the replication and transcription of viral RNA (Lan *et al.*, 2020). There are reports that the N protein can regulate the host cell cycle, including apoptosis, which helps the reproduction and spread of the virus (McBride *et al.*, 2014).

1.3. Mutations in the genome of the SARS-CoV-2 virus

The SARS-CoV-2 virus, due to its high mutation rate, is a constant threat to human health. This virus has multiple strains that have spread throughout the world (Khan *et al.*, 2022). Among such variations, one can single out the D614G mutation in the C-terminal region of the S1 domain (Nikonova *et al.*, 2021). Most strains with the D614G mutation also have a mutation in the protein responsible for replication, which can affect the rate of virus replication (Bhat *et al.*, 2021; Ou *et al.*, 2021).

There are also «disturbance options» associated with rapid spread in human populations. Such as, Alpha (B.1.1.7), Beta (B.1.351), Gamma (B.1.351), Delta (B.1.617.2) and Omicron, for example, Alpha variant was found in the UK at the end of 2020. Compared to other variants, it turned out to be 40-80% more contagious. And the Omicron variant (B.1.1.529), which appeared in 2021 in South Africa, turned out to be the fastest growing variant worldwide (Khan *et al.*, 2022).

2. Association of different genes and diseases with severe COVID-19

Patients with COVID-19 often have comorbidities such as hypertension, type 2 diabetes, and cardiovascular disease, those are risk factors for severely ill people. Differences in disease severity by gender have also been reported, with men most vulnerable to severe or fatal COVID-19 outcomes (Gemmati *et al.*, 2020). Other risk factors include, for example, smoking, chronic obstructive pulmonary disease (COPD) (Acevedo *et al.*, 2021), diet, physical activity, older age (>60 years) (Zhang *et al.*, 2020) and malignancies (Martínez-Gómez *et al.*, 2022). Genetic factors are also important, as understanding their contribution will provide insight into the outcomes of COVID-19.

2.1. Genes linked to cardiovascular disease and COVID-19

Cardiovascular disease is the world's leading cause of death, rising sharply with age. For patients with COVID-19, cardiovascular disease is associated with severe infection and higher mortality rates, especially heart failure and coronary artery disease. It is now reported that CVD susceptibility genes may also be associated with severe SARS-CoV-2 infection (Gallo Marin *et al.*, 2021).

The most studied genes in this regard are *ACE* and *ACE2*. The *ACE* gene is located on chromosome 17 (17q23.3) and is responsible for the synthesis of ACE (angiotensin-converting enzyme), it plays an important role in the regulation of blood pressure and electrolyte balance, promotes the conversion of angiotensin I to angiotensin II, which causes vasoconstriction, increased blood pressure and is the main regulator of aldosterone synthesis. Angiotensins I and II are components of the RAS system (renin-angiotensin system). The *ACE* gene has been fairly well studied, and most of the published data confirms the rs4340 (Alu I/D) polymorphism leading to the insertion (insertions, I) or loss (deletions, D) of the 289 bp Alu repeat, affecting ACE level in blood serum and tissues. In individuals who carry the I/I allele, it is minimal, and in individuals with the D/D allele, it is maximal (Elkina *et al.*, 2021). Deletion of the Alu repeat increases the expression of the *ACE* gene and leads to an increase in the concentration of ACE in the blood, lymph and tissues, which is a factor that increases the risk of developing cardiovascular diseases such as myocardial infarction, coronary heart disease, as well as the risk of kidney disease, atherosclerosis and Alzheimer's disease. Allele I is associated with increased body resistance to physical stress. A large number of studies have revealed the relationship between the D/D variant and the development of hypertension (Elkina *et al.*, 2021; Pinheiro *et al.*, 2019).

ACE D/D polymorphism is reported to be associated with obesity and diabetes, chronic conditions contributing to high risk of COVID-19 infection and poor outcomes (Sarangarajan *et al.*, 2021).

The human *ACE2* gene is located on the X chromosome Xp22.2 and encodes angiotensin converting enzyme 2. As previously mentioned, it is a functional cellular receptor for SARS-CoV and SARS-CoV-2. This gene is expressed in many organs and tissues. The rs2285666 genetic variant is one of the studied SNPs that can alter alternative mRNA splicing and affect the expression of ACE2 receptor genes. The functions of the ACE2 protein are the regulation of blood pressure and participation in the transport of amino acids. Genetic variants of *ACE2* are associated with the development of heart failure, myocardial infarction, and acute lung failure (Aziz & Islam, 2022; Gheblawi *et al.*, 2020; Jia, 2016; Martínez-Gómez *et al.*, 2022).

To date, numerous researches has been accumulated on the association of the *ACE* and *ACE2* genes with the severe course of COVID-19. For example, the results of a meta-analysis including 11 studies with 950 severe cases and 1573 non-severe cases of COVID-19 infection showed that *ACE* I/D rs1799752 and *ACE2* rs2285666 may increase the severity of the course in patients with COVID-19 (Aziz & Islam, 2022). Also, another meta-analysis found that carriers of *ACE* rs4646994 D/D genotype and *ACE2* rs2285666 G/G genotype had an increased risk of developing severe disease (Saengsiwaritt *et al.*, 2022). In a study of 146 patients with COVID-19 by scientists from Iran, it was found that the prevalence of the *ACE* rs4646994 D/D genotype was significantly higher in patients with severe COVID-19. And *ACE2* rs2285666 was not associated with disease severity (Najafi & Mahdavi, 2023). In a study in Mexican patients, with a sample of 53 healthy individuals and 165 patients who tested positive for COVID-19, divided into groups of asymptomatic, mild and severe disease, an association was found between the D/D polymorphism of the *ACE* gene and the severe course of COVID-19 (Mateos *et al.*, 2023). A 2022 study of 481 people with COVID-19 infection suggested that the T *ACE2* rs2285666 allele is a risk factor for severe and critical COVID-19 outcomes, especially for men, regardless of age, hypertension, obesity, and type 2 diabetes (Martínez-Gómez *et al.*, 2022). Also of interest are studies that report that different genetic variants may have different effects on susceptibility to COVID-19 in different populations. For example, the results of a meta-analysis showed that the D/D *ACE* rs466994 genotype increases the risk of susceptibility to COVID-19 by about 1.7-fold in Asian populations, and the G/G *ACE2* rs2285666 genotype may increase the risk of acute respiratory distress syndrome in Western countries (Keikha & Karbalaei, 2022).

However, there are publications that do not find a significant association with the severity of COVID-19 infection, for example, in a study by Celik et al. including 155 patients, no association was found between the *ACE* I/D and *ACE2* genes (rs2106809 and rs2285666) with the severity of COVID-19 infection (Karakaş Çelik *et al.*, 2021). In another study with 129 participants, a female to male ratio of approximately 1:1 concluded that there is a correlation between susceptibility of the G/G *ACE2* genotype (rs2285666) and the homozygous G/G *ACE* genotype (rs4343) to COVID-19 infection, but no affect on its severity. This statement, as the authors report, requires confirmation by studies with an even larger sample (Alimoradi *et al.*, 2022).

There are publications that focus on the *AGTR1* (3q24) gene, which encodes an angiotensin II receptor type 1 protein. Its main role is the regulation of blood pressure. The rs5186 polymorphism is of the greatest importance, leading to the A > C substitution at position 1166, which changes the nature of gene expression and regulation. This genetic marker is associated with arterial hypertension (Elkina *et al.*, 2021). In a study by Sabater Molina et al. the results did not show a significant association with respect to disease severity. However, the A/A genotype for rs5183 showed a higher risk of hospitalization in patients with comorbidities (hypertension or diabetes) (Sabater Molina *et al.*, 2022).

There is another interesting publication related to the *MAS1* gene, where they analyzed the exome in one family with COVID-19 and found that c.446C > T p. (S149L) in this gene was present only in a person with a severe form

of the disease. *MAS1*, encoding the Ang1-7 receptor, has an important function in the renin-angiotensin system (RAS) and has recently been reported to have a potentially protective role in COVID-19 disease. The authors of the paper hypothesized that this rare variant could impair its protective effect by downregulating the renin-angiotensin system, which could lead to severe disease (Azzarà *et al.*, 2022).

2.2. Association of Genes Involved in Obesity and COVID-19

Obesity is caused by fat deposits in large quantities in the subcutaneous tissue, organs and other tissues. Obesity can be both an independent multifactorial disease that occurs in most patients, and a syndrome that accompanies other diseases (Timasheva *et al.*, 2021). Early obesity has been said to be one of the risk factors for severe COVID-19. It is suggested that SARS-CoV-2 infection can cause inflammation and alter the function of adipose tissue. In obesity and diabetes, adipose tissue is at risk and may be involved in interactions with SARS-CoV-2. *ACE2* expression in adipocytes is increased in obese patients (Kruglikov *et al.*, 2020). When adipose tissue interacts with SARS-CoV-2, in which *ACE2* expression is higher compared to the lungs, it can become a reservoir for viral infections (Kruglikov & Scherer, 2020). The virus can also upregulate genes that are associated with lipid metabolism in lung epithelial cells (Al Heialy *et al.*, 2020). To explore whether infection of adipose tissue with SARS-CoV-2 contributes to pathogenesis, Martínez-Colón et al. were able to identify two cellular targets of infection, adipocytes and a subset of inflammatory macrophages. These data indicate that SARS-CoV-2 infection of adipose tissue can lead to disease severity by replicating the virus in adipocytes and inducing inflammation due to infection of macrophages (Martínez-Colón *et al.*, 2022).

2.3. Association of Genes Involved in Diabetes and COVID-19

Diabetes mellitus is a metabolic disorder characterized by an increase in blood sugar. The prevalence of diabetes has increased worldwide with lifestyle changes. About 90% of all cases of diabetes are type 2 diabetes. Only 1-2% of patients with mild SARS-CoV-2 infection have been reported to have pancreatic lesions, but 17% of patients with severe disease have pancreatic lesions, exacerbating the systemic inflammatory response and thus hastening the onset of acute respiratory distress syndrome (Lima-Martínez *et al.*, 2021; Liu *et al.*, 2020). Describing molecular pathways is essential for discovering therapeutic targets in diabetic patients infected with COVID-19 (Ni *et al.*, 2023).

Obukhov et al. hypothesized that dysregulation of the renin-angiotensin system is the underlying cause of the accompanying pathology between type 2 diabetes mellitus and severe SARS-CoV-2 infection (Obukhov *et al.*, 2020). Inflammation plays a major role in the etiology of type 2 diabetes and COVID-19. Loss of ACE2 in diabetes leads to a change in the phylogenetic composition of the gut bacterial community, leading to systemic inflammation (Duan *et al.*, 2019; Obukhov *et al.*, 2020). In patients with diabetes, with COVID-19 disease, the development of pneumonia can be dangerous, due to pre-existing systemic inflammation, multiple organ failure can develop. As you know, a cytokine storm can be caused by inflammation of the intestine and damage to the lungs (Kruglikov *et al.*, 2020). Wu et al. identified two common genes, *ABO* and *NUS1* for type 2 diabetes mellitus and COVID-19, associated with immune function and chemokine activation status. Also, in this study it is said that there are common chemokine receptors between these diseases - these are CCR2 and CCR3. The researchers conclude that certain chemokines and their receptors involved in the cytokine storm may lead to hyperinflammation in type 2 diabetic patients infected with SARS-CoV-2 (Wu *et al.*, 2022). The type I interferon response (INF, INF-α, and INF-β) induces the expression of various interferon-stimulated genes (ISGs) that confer antiviral activity on host cells, but inappropriate activation may exacerbate inflammation, which is the underlying mechanism of diabetes mellitus 2 type and severity of COVID-19 (Ni *et al.*, 2023). There are also suggestions that microRNA is an important

link between diabetes and the severity of COVID-19. (Bhavya *et al.*, 2022; Ni *et al.*, 2023). An increase in IL-6 levels has been seen in diabetic patients with COVID-19 (Lima-Martínez *et al.*, 2021).

2.4. Blood System Gene Association and COVID-19

The *ABO* gene encodes a protein that is a glycosyltransferase enzyme. This gene determines a person's blood group by modifying oligosaccharides on cell surface glycoproteins. It is known that differences in blood group antigen expression can increase or decrease host susceptibility to many infections. Some blood groups can alter the innate immune response to infection (Cooling, 2015). Using a genome-wide study in 2020, an association of the *ABO* gene (9q34.2) (rs657152) with the severity of COVID-19 was found (Ellinghaus *et al.*, 2020). A high risk of respiratory failure was found in individuals with blood type A. In contrast, patients with blood type O had the lowest risk (Ellinghaus *et al.*, 2020; Zhao *et al.*, 2021). Such data suggest that individuals with blood type O, who have neither A nor B antigens, are protected from viral infection (Niemi *et al.*, 2022). The *ABO* variant is thought to be associated with higher levels of the CD209 protein, which appears to interact directly with the SARS-CoV-2 spike protein (Karim *et al.*, 2021; Niemi *et al.*, 2022). However, there are a number of studies where the association with the severe course of COVID-19 has not been identified (Dzik *et al.*, 2020; Latz *et al.*, 2020).

2.5. Involvement of the 3p21.31 locus in severe COVID-19

In June 2020, a large international team of scientists analyzed the genomes of 1980 people from Italy and Spain and found that the *ABO* blood type locus and chromosome 3 gene cluster (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*) are associated with the development of COVID-19 respiratory failure. For example, for the *LZTFL1* gene, G/A rs11385942 served as a risk allele, leading to strong expression in human lung cells (Ellinghaus *et al.*, 2020). We now know that this chromosome 3 gene locus was inherited by us from Neanderthals about 50,000 years ago. Due to this genetic heritage, approximately 16% of people from Europe and 50% of people from South Asia carry these genes (Zeberg & Pääbo, 2020). Also, confirmation of the genetic association of the 3p21.31 locus with severe COVID-19 was obtained by another independent GWAS, increasing the significance of this locus in susceptibility to the disease, and in addition, new risk variants were reported in other chromosomes (Pairo-Castineira *et al.*, 2020). Consider the *LZTFL1* gene, which encodes a protein expressed in many places. It is localized in the cytoplasm. LZTFL1 is a known inhibitor of the epithelial-mesenchymal transition (EMT). Its protein interacts with the proteins of the Bardet-Biedl syndrome (BBS), thereby regulating the transport of proteins to the ciliary membrane. Usually, the *LZTFL1* gene is expressed in lung epithelial cells, where ciliated epithelial cells are also located, which are considered the main cellular targets in COVID-19 disease (Downes *et al.*, 2021; Niemi *et al.*, 2022; Ravindra *et al.*, 2021). A study by Downes et al. shows that *LZTFL1* is a candidate for association with severe COVID-19 disease, the results suggest that rs17713054 is a variant of the enhancer motif with an increase in function, leading to increased expression of *LZTFL1* and, as a consequence, leads to worse disease outcomes. The authors concluded that *LZTFL1* could be a possible target for the treatment or prevention of SARS-CoV-2 infection (Downes *et al.*, 2021).

In Russia, locus 3p21.31 was also studied along with the *ABO* gene, for example, the results of a study by Balanovsky et al. show that high frequencies of the risk alleles rs11385942 and rs657152 are found among Europeans and South Asians compared with other world populations. Genetic differences between different peoples also contribute to the heterogeneity of the disease in the world (Balanovsky *et al.*, 2021). In addition, Balanovska et al. The spatial variability of SNP markers of the *LZTFL1* gene was studied in the indigenous population of Russia and the world (Balanovska *et al.*, 2022). An interesting study by Ekomasova et al., where the distribution of polymorphic variants

of genes associated with severe SARS-CoV-2 infection, including the *LZTFL1* and *ABO* genes, in Permsky, Burzyan and Arkhangelsky Bashkirs populations living in Russia (Ekomasova *et al.*, 2023).

Also, chemokine receptor genes are located at the 3p21.31 locus, one of which is the *CCR5* gene, which is expressed by cells of the immune system, so Cantalupo et al. conducted a study that identified three SNPs (rs9845542, rs12639314 and rs35951367) implicated in severe COVID-19 using whole exome sequencing (WES) in 147 patients. Their results demonstrate the biological role of *CCR5* in the progression of COVID-19 (Cantalupo *et al.*, 2021).

2.6. Involvement of the 12q24.13 locus in COVID-19

Recent studies report that a locus on chromosome 12 (12q24.13) contains three genes encoding antiviral 2',5'-oligoadenylate synthetase (OAS) enzymes (*OAS1, OAS2*, and *OAS3*) associated with susceptibility to COVD-19 (COVID-19 Host Genetics Initiative, 2021; Pairo-Castineira *et al.*, 2020). The proteins encoded by these genes are induced by interferons and activate the latent form of RNase L. Activation of this pathway leads to degradation of viral RNA and suppression of viral replication (Sadler & Williams, 2008). The RNase L pathway is particularly important for the immune response to SARS-CoV-2. So, for example, in one study, it is said about the study of the relationship of this locus and its influence on the severity of the course of COVID-19, which compared hospitalized and non-hospitalized patients of European and African origin. Interestingly, their results from clinical trials show that pegIFN-λ1 interferon treatment accelerated virus clearance in all patients, however, individuals with a risk *OAS1* haplotype (AAA for rs1131454-A, rs10774671-A, and rs2660-A) benefited most from this treatment. Type I interferons (IFNβ-1a and IFNα2b) are also reported to be being tested as an early treatment for SARS-CoV-2 infection with promising results. The authors of this study also suggested that non-risk G alleles of two variants, rs10774671 and rs1131454, protect *OAS1* transcripts from nonsense-mediated decay. Conversely, the A risk alleles of both variants create an isoform that will be vulnerable to nonsense-mediated decay and low expression (*OAS1-p42*) (Banday *et al.*, 2022).

2.7. Involvement of the HLA genes in COVID-19

HLA genes (Human Leukocyte Antigens) are located on the 6th human chromosome, these genes are divided into three classes. The main function is to present the antigen on the surface of the plasma membrane for recognition by immune cells. They are also involved in cell recognition, initiation and implementation of the immune response. As a result, *HLA* alleles can influence susceptibility to certain diseases. HLA class I antigens play an important role in the development of a specific immune response to viral infections (Arab *et al.*, 2023; Dobrijević *et al.*, 2023; Golota *et al.*, 2021). There are currently many studies on different *HLA* alleles that are involved in the susceptibility or severity of COVID-19. For example, the results of a study by Weiner et al. showed that carriers of *HLA-C*04:01* are associated with severe disease and susceptibility to COVID-19 (Weiner *et al.*, 2021). Dobrijević et al. based on their meta-analysis, presented different *HLA* alleles associated with the severity of COVID-19 or with its lethal outcome. These included alleles of the *HLA-A, -B, -C, -DRB1* and *-DQB1* loci, which are potential biomarkers of COVID-19 severity (Dobrijević *et al.*, 2023).

2.8. The role of Cytochrome P450 genes in the treatment of COVID-19

Knowledge of how certain genes affect the development can be used in the treatment of COVID-19, for example, the study of different variants of cytochrome P450 (CYP450s) genes that encoding enzymes involved in many cellular processes such us the metabolism of phase 1 xenobiotics, toxins and drugs. CYP450 enzymes are localized substantially in the liver, but can be found in the small intestine, lungs, kidneys, and heart (Fatunde *et al.*, 2020). In terms of distribution, the most common enzymes are CYP3A4 and CYP2D6 (Stavropou-

lou *et al.*, 2018). Cytochromes P450 are also being studied in cancer research and cancer treatment (Harvey *et al.*, 2014). It is important to know the specificity of enzymes and their regulatory mechanisms for accurate drug dose determination (Stavropoulou *et al.*, 2018). Cytochrome P450 inhibitor drugs are used to treat patients with COVID-19, such drugs as azithromycin and hydroxychloroquine (Fakhouri *et al.*, 2020). The *CYP2D6* and *CYP2C19* genes were responsible for most treatment modifications, and the medications most often affected were ondansetron, oxycodone, and clopidogrel, commonly given to patients with COVID-19 (Stevenson *et al.*, 2020). Also, a population study by Dzhaubermezov et al. shows the distribution of alleles and genotypes frequencies of the *CYP2D6* (rs3892097, rs4986774, rs1065852) and *CYP1A1* (rs1048943) genes in the Finno-Permian peoples living in the European part of Russia. Such data are useful for epidemiological purposes (Dzhaubermezov *et al.*, 2022).

2.9. The role of DPP9 gene in the COVID-19

DPP9 gene (dipeptidyl peptidase 9) (19p13.3). This gene encodes a serine protease, which is part of the dipeptidyl peptidase (DPPs) family. At present, DPP9 has received a lot of attention, as DPP9 inhibitors cause pyroptosis of immune cells. DPP9 is predominantly localized in the cytoplasm and nucleus. DPP9 is involved in cell adhesion and migration, energy metabolism, and antigen presentation, and blocks the C-terminus of the pyrine domain of the NLR family to inhibit the activation of inflammasomes responsible for activating the inflammatory response. (Cui *et al.*, 2022; Griswold *et al.*, 2019; Pairo-Castineira *et al.*, 2020). Results of a study by Sharif-Zak et al. showed that *DPP9* expression was higher in patients with SARS-CoV-2 infection. It was found that male patients with severe disease expressed more *DPP9* than female patients with the same form of the disease (Sharif-zak *et al.*, 2022). DPP9 is associated with pulmonary fibrosis, which is one of the concomitant features of severe COVID-19. However, the role of *DPP9* is not completely clear in the development of COVID-19. The study of the mechanism of action of DPP9 will shed light on the possible prevention and treatment of this disease (Cui *et al.*, 2022).

The results of a genome-wide association study in 2,244 patients with severe COVID-19 clinical outcome showed new significant associations across the genome, namely the *DPP9* gene and the *IFNAR2* and *TYK2* genes discussed below (Pairo-Castineira *et al.*, 2021).

2.10. The role of TYK2 gene in the COVID-19

The *TYK2* gene (19p13.2) encodes tyrosine kinase 2. It belongs to the Janus (Jaks) family of protein tyrosine kinases. TYK2 binds to interferon receptors (IFN)-α, IFN-β and some interleukins. Jak dimers promote attachment, phosphorylation of STAT proteins. And they, in turn, can affect the regulation of genes associated with the production of pro-inflammatory cytokines and growth factors (Levy *et al.*, 2022). The Jak/STAT pathway plays an important role not only in many physiological processes, but also in pathological ones, such as in inflammatory diseases. Which makes this pathway a potential target for therapeutic purposes (Rusiñol & Puig, 2023). *TYK2* was studied early as a possible therapeutic target for autoimmune diseases and cancer (Niemi *et al.*, 2022). Plays a significant role in regulating immune responses against infectious diseases. In 2023, an article was published that first reported the association of the *TYK2* SNP (T rs2304255 allele, rs12720354 A allele, and rs12720207 G allele) with the severity of COVID-19. The scientists found that these alleles are associated with low expression of *TYK2*, showing its essential role in the immune response (Zabihi Rizi *et al.*, 2023). The use of TYK2 inhibitors has great potential for COVID-19, as baricitinib has been approved for the treatment of patients with this disease (Muromoto *et al.*, 2021).

2.11. The role of IFNAR2 gene in the COVID-19

The *IFNAR2* (interferon alpha and beta receptor subunit 2) gene (21q22.1) encodes an interferon receptor that is involved in type I interferon signaling and is vital for innate antiviral

defense. IFNAR2 is involved in the activation of the Janus receptor protein kinases mentioned above, which are responsible for phosphorylation of the STAT1 and STAT2 proteins. Type I interferons are considered to be possible potential options for the treatment of patients with COVID-19 (Schreiber, 2020). IFNAR2 has been reported to play a protective role in COVID-19, as increased expression of the *IFNAR2* gene reduced the likelihood of severe COVID-19 and, conversely, rare mutations with loss-of-function (LOF) in *IFNAR2* are associated with severe course of COVID-19 (Pairo-Castineira *et al.*, 2020). Smieszek et al. in their study report an increased susceptibility to severe SARS-CoV-2 infection with loss-of-function mutations in the *IFNAR2* gene, in particular among the Asian population, where the mutation is more common (Smieszek *et al.*, 2021).

Conclusion

Thus, genetic polymorphisms associated with risk of developing certain diseases can also serve as markers as to the severity of COVID-19. By studying human genetics, researchers will be able to gain more insight regarding both individual and population-wide patterns of COVID-19 disease, including the causes of different clinical outcomes of the disease. Furthermore, such knowledge will be extremely useful in the research and development of new drugs. The study of the distribution of polymorphic variants of genes associated with infectious diseases will expand the database on this topic. A certain understanding will be formed of how different gene variants affect the clinical outcomes of the disease and how they are distributed among various populations of the world.

Population-based studies of the prevalence of risk alleles and genotypes will make it possible to adjust the epidemiological prognosis and to be better prepared for other infectious disease outbreaks in the future, particularly in certain regions where populations are more susceptible to diseases and obesity.

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